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Neuro-oncology

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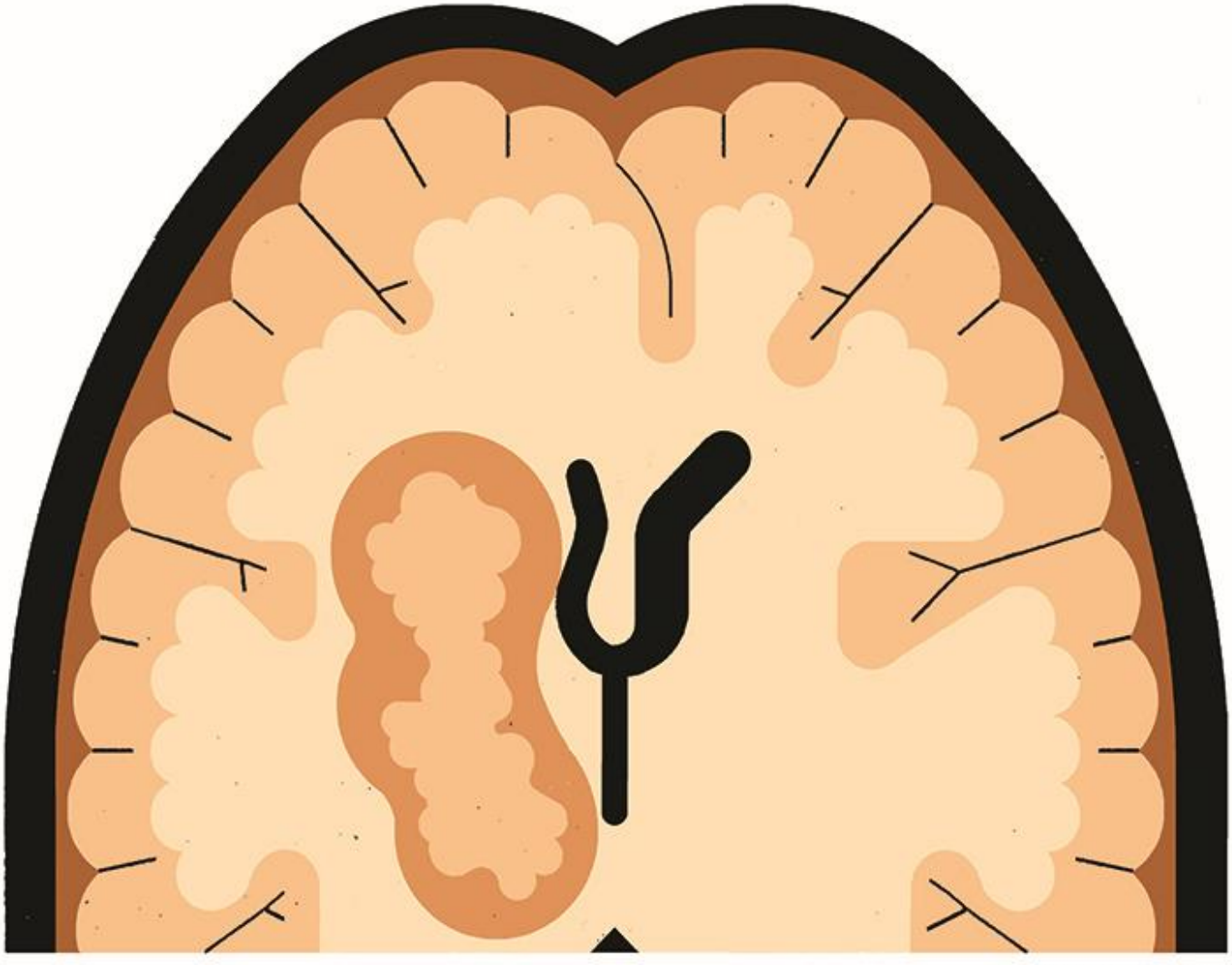

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Neuro-oncology

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EDITOR'S PREFACE

Neurology and Language, In Motion

The language of medicine is utilitarian by necessity, but it has its charms. The logical architecture of medical terminology is just as aesthetically appealing as the strange ornaments that decorate our clinical notes (singultus, anamnesis, encephalomyeloradiculoneuropathy). Like all languages, our clinical vernacular has evolved. Over time, medical nomenclature has rightly moved away from naming diseases after people and places, now emphasizing objective pathophysiologic features of disease. Arbitrary lettering and numbering systems have proliferated.

Since the last *Continuum* neuro-oncology issue in 2020, there have been seismic changes in our understanding, and by extension naming, of brain tumors. The 2021 *World Health Organization Classification of Tumors of the Central Nervous System* overhauled the names of many familiar and some newly recognized brain tumors. Oncologic identity and behavior are increasingly better characterized by the tumor genotype and protein expression than by histologic appearance alone.

The simple, poetic, dactylic pentameter of oligodendroglioma and medulloblastoma has given way to oligodendroglioma, *IDH*-mutant and 1p/19q-codeleted, and medulloblastoma, SHH-activated, TP53-wildtype. While the pathophysiologic precision is a clear improvement, many of the new names do not exactly roll off the tongue. To the extent that language provides a scaffold for cognition, some of the new terminology may simply be more challenging to learn. In any case, unless and until the nomenclature evolves further, we will need to be familiar with the modern classification so we can deliver the best possible care to our patients.

Speaking of the power of language, this issue of *Continuum* is packed with brilliant insights written by expert authors, recruited and organized by our guest editor Dr Lakshmi Nayak. The issue leads off with a herculean summary of the new brain tumor classification system including the molecular techniques needed to characterize brain tumors, authored by Drs David M. Meredith and David J. Pisapia. Dr Macarena I. de la Fuente provides a concise yet comprehensive overview of the adult-type diffuse gliomas. The particular features of pediatric neuro-oncologic disorders are thoroughly covered by Dr Fatema Malbari. The protean manifestations of central nervous system lymphoma receive a comprehensive review from Dr Lauren Schaff. Drs Priya Kumthekar and Emilie Le Rhun outline the many complexities of brain metastases and leptomeningeal disease. Skull base tumors, including the ubiquitous meningioma, are reviewed by Drs Deborah A. Forst and Pamela S. Jones.

The direct effects of tumors are only part of the impact of neuro-oncologic disease. Dr Jerome J. Graber provides a comprehensive discussion of the growing list of recognized paraneoplastic neurologic syndromes. The many neurologic complications of conventional chemotherapy and radiation therapy are thoughtfully summarized by Dr Jennie W. Taylor. Dr Nancy Wang outlines the increasingly recognized neurologic complications of cancer immunotherapies. Finally, among the clinical reviews, Dr Mary R. Welch deftly outlines the management of complications in patients with neuro-oncologic disorders. The Selected Topics in Neurology Practice article in this issue appropriately addresses the pressing importance of palliative care

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and care partner support in neuro-oncology settings, authored by Dr Akanksha Sharma.

After reading or listening to the content in this issue, subscribers can obtain up to 20 AMA PRA Category 1 Credits™ toward self-assessment CME or, for Canadian participants, a maximum of 20 hours toward the Self-Assessment Program [Section 3] of the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada with our posttest, written by Drs Adam Kelly and Allyson R. Zazulia.

As the language of neurology has changed, so too has the medium by which it's shared. Since 2012, *Continuum* subscribers have had access to *Continuum* Audio, which delivers *Continuum* content in the form of audio interviews with our expert authors. I am happy to share that beginning in 2024, *Continuum* Audio will launch on all major open podcast platforms, including Apple, Spotify, Google, and Amazon. Improving access to *Continuum* content is one of my priorities as editor-in-chief of the journal, and our entire editorial team is excited to make this change. Prior interviews, including those for this issue, will remain posted at the article level on ContinuumJournal.com, on the *Continuum* Audio online platform, and the mobile app until the end of 2024. Verbatim audio recordings of each article will be available to subscribers only through *Continuum* Read Aloud, which will be rebranded as *Continuum* Aloud in 2024. These recordings are found at the article level at ContinuumJournal.com and in the AAN's Online Learning Center at continpub.com/CME.

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The perpetual motion of neurology is one of many reasons our field is such an exciting specialty to practice. At *Continuum*, we look forward to keeping you at the cutting edge of neurology so you can deliver the best possible care to your patients.

—LYELL K. JONES JR, MD, FAAN
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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

2021 World Health Organization Classification of Brain Tumors

By David M. Meredith, MD, PhD; David J. Pisapia, MD

ABSTRACT

OBJECTIVE: **The classification of brain tumors is a rapidly evolving field that requires extensive integration of molecular diagnostic findings from an expanding set of platforms and assays. This article summarizes the schema presented in the 5th edition of the World Health Organization (WHO) classification of central nervous system (CNS) tumors while highlighting diagnostic molecular findings and discussing the strengths and weaknesses of commonly available testing modalities.**

LATEST DEVELOPMENTS: **Several major changes in practice were introduced with the 5th edition of the CNS WHO classification, including molecular grading of adult diffuse gliomas, the introduction of many new entities within the spectrum of pediatric gliomas and glioneuronal tumors, and the widespread adoption of methylation classes as useful or even necessary diagnostic criteria. Additionally, several revisions to nomenclature (eg, *IDH*-mutant gliomas) were introduced for simplicity and to disambiguate from other tumor types.**

ESSENTIAL POINTS: **The classification of brain tumors continues to grow in complexity alongside our improved understanding of their nuanced molecular underpinnings.**

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INTRODUCTION

The development of a diagnostic framework that delivers clinically relevant information is a continually evolving and iterative process. The goal is that predicted biological outcomes indicated by specific diagnostic entities approximate actual outcomes in a way that informs patient and provider expectations and guides treatment management strategies. The newest edition of the *World Health Organization* (WHO) *Classification of Tumors of the Central Nervous System* (CNS)[1] reflects the rapidly evolving field of surgical neuropathology. It makes explicit the undeniable trend of the last 2 decades that entity-defining diagnostic criteria are shifting away from standard morphological features interpreted under the light microscope and toward molecular diagnostic criteria defined at the level of nucleic acids and

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proteins. This shift has been driven by next-generation sequencing technologies that have revealed recurrent alterations in tumors with shared morphological, anatomical, and demographic features. Incorporating these data into clinical practice is enabled by increasing access to lower-cost next-generation sequencing assays at academic centers and through commercial laboratories. Moreover, in the last 5 years newer molecular modalities that test for the presence or absence of epigenetic biomarkers, including methylation array profiling, have initiated a revolution in neuropathology and are likely to become pervasive in pan-cancer oncologic practice.

In this article, we highlight the more common CNS tumors with a focus on the concepts and molecular features that have led to shifts in the WHO-endorsed classification systems. First, a few of the more straightforward WHO changes should be mentioned for clarity. These include a change in grading nomenclature from Roman numerals (I-IV) to Arabic numerals (1-4). Terms such as *anaplastic* that were used in many ways as a redundant marker of tumor grade have been dropped in most instances. For example, what was once an *anaplastic oligodendroglioma, WHO grade III* is now referred to as *oligodendroglioma, CNS WHO grade 3* or, as discussed later, in its more complete form, *oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 3*.

A useful way to consider primary glial neoplasms of the CNS is to distinguish between those that are "diffuse" from those that tend to be well circumscribed. The former category presents with ill-defined surgical margins where tumor cells infiltrate surreptitiously throughout the brain parenchyma. This feature makes them intrinsically difficult to resect and, at present, the majority recur. Radiologic features of regions corresponding to areas of lower histologic grade may show in situ expansion of the underlying brain architecture, nonenhancement following the administration of contrast, and T2-weighted hyperintensity that may mimic or co-occur with edema. Regions corresponding to higher histologic grades may show enhancement following the administration of contrast.

Over the last 15 years, DNA alterations in tumors commonly occurring in children and adults have been found to be quite distinct, even in cases that share similar histomorphologic features. The 2021 WHO CNS tumor classification has thus introduced the explicit terms *adult-type* and *pediatric-type* gliomas to refer to these tumor classes while allowing for the possibility that an adult-type glioma may occasionally present in a child, and vice versa. In addition to outlining the many changes in the 2021 WHO CNS tumor classification system, this article summarizes the molecular diagnostic tools now required to characterize many of these tumors.

KEY POINTS

- **The majority of central nervous system (CNS) tumors possess highly characteristic genetic and epigenetic profiles, which are usually required to be integrated with histology for accurate classification.**
- **Single-gene tests, such as immunohistochemistry, fluorescence in situ hybridization, and polymerase chain reaction are rapid and cost-effective assays when a specific CNS tumor diagnosis or alteration is suspected.**

DIAGNOSTIC MOLECULAR ASSAYS

As increasingly detailed molecular profiling is necessary not only for the precise classification of CNS tumors but also for trial enrollment and targeted therapy planning, a wide variety of molecular assays have been developed and adopted in both academic and commercial settings to serve these needs. Below is a brief discussion of the capabilities and best uses of several of the most widely used tools.

Immunohistochemistry

The development of variation-specific antibodies has permitted rapid and accurate assessment of many tumors characterized by diagnostically or

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therapeutically relevant gene variation events. Notable examples, which will be described in subsequent sections, include IDH1 R132H, H3 K27M, and *BRAF*^{V600E}. Many other existing markers may also be aberrantly upregulated or downregulated in response to characteristic genomic alterations, such as loss of ATRX expression in *IDH*-mutant astrocytomas, loss of INI1 expression in atypical teratoid/rhabdoid tumors, or nuclear translocation of β-catenin in SHH-activated tumors. The advantages of immunohistochemistry include rapid turnaround time (usually less than 24 hours), ubiquitous technology, and low cost (approximately $40 per stain). However, diagnostic immunohistochemistry is only available for a relatively limited number of tumors, and many stains are difficult to perform or interpret consistently.

Fluorescence In Situ Hybridization

Similar to immunohistochemistry, FISH has been employed for many decades and may be utilized in select instances where highly specific gene rearrangements or copy number changes are diagnostic. For example, FISH has long been the gold standard test for 1p/19q codeletion assessment. Break-apart probes are highly effective at demonstrating gene fusions or rearrangements and can be used to confirm the presence of such an event suggested by microarray or sequencing analysis. The cost of FISH analysis can be as low as $100 per sample and turnaround times vary from 1 to 7 days depending on source material and technique. Given that most probes range from 150 kb to 500 kb in length, precise determination of fusion partner or amplicon size is generally not possible without using multiple probes. Conversely, FISH analysis may yield false-positive results in situations where larger genomic regions must be assessed, such as in tumors with focal instead of whole-arm 1p/19q losses.[2]

Polymerase Chain Reaction

Polymerase chain reaction assays are another set of single-gene tests that in general provide rapid turnaround times and highly sensitive screening. These tests, using either droplet digital or reverse transcriptase methods, focus on a small region of a gene that contains specific gene variation hotspots, such as codons 132 and 172 in *IDH1* and *IDH2*, respectively. These tests may often be performed in combination with or in place of more comprehensive assays when tissue is limited or results for a particular variation (eg, *BRAF*^{V600E}) are needed for rapid treatment planning. The cost for such tests is generally less than $200 per sample.

Chromosomal Microarray

Chromosomal microarray is a dedicated high-resolution genome-wide copy number assay. Many institutions offer single-nucleotide polymorphism array testing for both neoplastic and constitutional genomic testing, which carries the additional advantage of ploidy and copy-neutral loss of heterozygosity assessment. Given the prevalence of diagnostic and prognostic copy number changes in gliomas (eg, +7/-10, *CDKN2A* deletion, 1p/19q codeletion, C19MC amplification), chromosomal microarray testing has particular value for CNS tumors. Although chromosomal microarrays cannot detect balanced translocations, the majority of relevant fusion events in brain tumors result from focal intrachromosomal duplications or deletions (eg, 3′ duplication of *BRAF* producing the characteristic *KIAA1549::BRAF* fusion in pilocytic astrocytomas)

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that can be easily detected with this technology. Unlike the above tests, chromosomal microarray analysis is more dependent on a sample's tumor content, and the complexity of results increases turnaround time, which can be around 2 weeks.[3]

Next-Generation Sequencing Platforms

A wide variety of next-generation sequencing platforms have been developed in both commercial and academic settings, ranging from small panels to whole-exome coverage. Most centers have adopted medium-sized custom panels covering 150 to 500 genes of interest, often with additional intronic regions where hotspot breakpoints occur in common fusion events. These tests are also capable of detecting amplification and deletion events, and larger panels may offer comparable copy number detection as microarrays.[4] While most next-generation sequencing platforms are DNA-based, additional dedicated RNA platforms are available using either amplicon or hybrid capture methods to detect a wider variety of targeted fusion events. These assays generate large amounts of data that require extensive processing and bioinformatic analysis. As a result, testing can cost up to several thousand dollars and take several weeks to generate results. Nonetheless, the wealth of data next-generation sequencing testing offers makes it an appealing choice for routine testing of CNS tumors, especially those occurring in pediatric populations where diagnostic and targetable alterations are most prevalent.

Methylation Array

In 2018, a seminal article showed that array-based DNA tumor methylation profiling combined with machine-learning techniques can robustly characterize and classify a diverse set of CNS tumors.[5] Moreover, methylation profiling over many cases followed by unsupervised clustering has played a key role in fine-tuning the taxonomical hierarchy of CNS tumors. The effect may be one of "lumping" or "splitting." A salient example of the lumping phenomenon is the creation of a new diagnosis, *embryonal tumor with multilayered rosettes*, which encompasses three entities previously considered to be distinct based on histologic patterns (embryonal tumor with abundant neuropil and true rosettes, ependymoblastoma, and medulloepithelioma). On the other hand, clinically relevant subcategories of historically solitary entities have emerged (ie, splitting), exemplified by the evolution of well-defined medulloblastoma subtypes. These entities are described in detail in later sections.

Several entities within the 2021 WHO CNS tumor classification are now defined by their methylation profile. Examples are the newly defined *high-grade astrocytoma with piloid features*, where a methylation match is required for the diagnosis, the entity *CNS neuroblastoma, FOXR2-activated* where a methylation match is considered sufficient (given compatible histology) but not required, and many examples whereby a methylation match is considered "desirable" to make the diagnosis, but not required (eg, for the entity *diffuse glioma, MYB- or MYBL1-altered*).

As data continue to be collected, methylation profiling and the development of classifiers suited to particular diagnostic contexts are being developed, including meningioma classifiers,[6] sarcoma classifiers,[7] and metastatic tumors of unknown primary origin.[8]

KEY POINTS

- Comprehensive profiling of CNS tumors via chromosomal microarray or next-generation sequencing panels is frequently needed to resolve more complex differential considerations and to classify tumors with variable genetic profiles.
- Methylation profiling of CNS tumors has proven highly valuable for the creation of machine learning–based classifiers, and some tumor types cannot be accurately classified without obtaining a methylation profile.
- Adult diffuse gliomas are largely classified on the basis of *IDH1/2* and 1p/19q codeletion status, irrespective of microscopic appearance.

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ADULT-TYPE DIFFUSE GLIOMAS

The discovery of recurrent variations involving isocitrate dehydrogenase (IDH) encoded by *IDH1* and more rarely *IDH2* in diffuse gliomas has transformed our understanding of tumors that historically comprised diffuse astrocytomas (including glioblastomas), oligodendrogliomas, and oligoastrocytomas. While the initial discovery of *IDH* gene variations in gliomas was made in a subset of glioblastomas,[9] it was immediately apparent that those "glioblastomas" with *IDH* variations were quite different from their *IDH*-wildtype counterparts. They tended to occur in younger adults and arose from lower-grade tumors that had presented years earlier. This led to the discovery that a high percentage of tumors that had been diagnosed as lower-grade diffuse astrocytomas and oligodendrogliomas harbored *IDH* variations.[10,11] Combined with the discovery that 1p and 19q chromosomal deletions were characteristic of tumors with oligodendroglial morphology,[12] the stage was set to define three major classes of adult-type diffuse gliomas,[13] a classification structure which became officially codified in its mature form only in 2021. While each has typical morphological features, they are now defined primarily using molecular criteria, with histologic features being retained (for now) to fine-tune tumor grading. The three classes of tumors are summarized in TABLE 1-1.

Astrocytoma, *IDH*-Mutant

A diffuse glioma with an *IDH* gene variation and that lacks 1p/19q codeletion is now the gold standard diagnostic definition of this tumor. In about 90% of cases, the *IDH* variation can be detected quickly with immunohistochemical staining for IDH1-R132H, the peptide product of the most commonly encountered missense variation in the gene, with a commercially available antibody against the altered epitope. However, in approximately 10% to 15% of cases, the variation is only detected clinically by sequencing the *IDH1/IDH2* genes, which may reveal R132C/G/S/L substitutions, and rarely *IDH2* R172K/M/W variations, where

TABLE 1-1 **The Three Main Categories of Adult-type Diffuse Gliomas**[a]

Adult-type diffuse glioma category	World Health Organization central nervous system tumor grade[b]		
	2	3	4
Astrocytoma, IDH-mutant	No mitoses	Mitoses	Microvascular proliferation, necrosis, *CDKN2A* homozygous deletion
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	Some mitoses	Increased mitoses, microvascular proliferation, *CDKN2A* homozygous deletion	-
Glioblastoma, IDH-wildtype	-	-	Microvascular proliferation, necrosis, *TERT* promotor variation, *EGFR* amplification, combined presence of relative gain of chromosome 7 (eg, trisomy 7) with relative loss of chromosome 10 (monosomy 10)

[a] Data from Louis DN, et al, Neuro-Oncol.[1]
[b] A dash indicates that no such entity or grade combination exists.

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codon 172 of *IDH2* encodes the analogous functional site of the protein as the R132 codon in *IDH1*. Interestingly, non-R132H variations are correlated somewhat with anatomical distribution, such as with non-R132H variants showing enrichment in those rare but increasingly recognized IDH-mutated tumors presenting in the brainstem or cerebellum.[14]

IDH in cancer becomes oncogenic due to a shift in the metabolic proclivities of the enzyme through a hotspot gain-of-function variation. Whereas wildtype IDH proteins preferentially accept isocitrate as a substrate to produce α-ketoglutarate, the variant gene yields a heterodimeric enzyme that accepts α-ketoglutarate (the usual product) as a substrate and produces the oncometabolite, 2-hydroxyglutarate, which is ordinarily foreign to the cell in any appreciable concentration. 2-hydroxyglutarate proceeds to wreak havoc in the cell in part through epigenetic dysregulation by competing with α-ketoglutarate itself as a coregulator to enzymes mediating the methylation status of nucleic acids and histones.

IDH variation, however, does not appear to be sufficient for gliomagenesis and requires several coconspirators. In the case of *astrocytoma, IDH-mutant*, these are typically *TP53* and *ATRX*. In fact, loss of ATRX expression by immunohistochemistry is a reliable surrogate for excluding 1p/19q codeletion given its mutual exclusivity with that alteration. Thus, in practice immunohistochemistry alone often provides sufficient confidence in establishing a diagnosis of *astrocytoma, IDH-mutant:* strong cytoplasmic labeling for IDH1-R132H is highly sensitive and specific for the R132H variation; diffuse and strong nuclear labeling for p53 is a reliable predictor of *TP53* missense variations; and loss of usually ubiquitous ATRX nuclear labeling is highly predictive of a truncating *ATRX* variation.

With a diagnosis of *astrocytoma, IDH-mutant* assured, the pathologist is still tasked with designating a CNS WHO grade. While historically grade assignment was purely a histologic endeavor, times have changed. Just as molecular findings may dictate the tumor class itself, they may also dictate tumor grade within a class. The detection of homozygous deletion of the *CDKN2A* locus, located on the short arm of chromosome 9 and encoding the well-described tumor suppressors p16-INK4A/p14ARF, is sufficient for a designation of CNS WHO grade 4 in this class. In fact, deletion of this locus as a harbinger of poor outcomes is somewhat of a recurring theme in CNS tumors, as we shall see in subsequent sections. Even in the absence of *CDKN2A* loss, however, a grade of 4 is assigned in the presence of microvascular proliferation, necrosis, or both. Keen observers will note that in the past (circa 2016) such neoplasms would have been called *glioblastoma, IDH-mutant*. The new standard is that these neoplasms are termed *astrocytoma, IDH-mutant, CNS WHO grade 4,* and the term *glioblastoma* is reserved for adult-type *IDH*-wildtype tumors. This reflects the well-established, dominant, and independent prognostic value of *IDH* status in diffuse gliomas, exemplified by the fact that even grade 4 *IDH*-mutated astrocytomas have an average survival time that is approximately 3 times longer than that of their *IDH*-wildtype counterparts (ie, bona fide glioblastomas). The distinction between grades 2 and 3 is still primarily one of mitotic activity. However, the prognostic utility of this distinction in the era of uniform assessment of *IDH1/2* and 1p/19q alterations is significantly diminished and questionable.[15]

Oligodendroglioma, *IDH*-Mutant and 1p/19q-Codeleted

Uniform infiltrating cells with round, regular nuclei and perinuclear clear halos accompanied by delicate branching vasculature and calcifications, the

KEY POINTS

- **A triple-variant immunohistochemical pattern (IDH1 R132H+, ATRX-, p53+) is highly specific for *IDH*-mutated astrocytomas, and formal demonstration of 1p/19q status is not necessary when present.**
- **Given the rate of false-positive 1p/19q codeletion results by fluorescence in situ hybridization, whole-arm testing of 1p and 19q via microarray or next-generation sequencing is recommended for oligodendrogliomas.**

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prototypical oligodendroglial morphological features sufficient for a diagnosis of oligodendroglioma in years past, are now superseded by the detection of *IDH* variation and 1p/19q codeletion. The co-occurrence of these alterations is now both mandatory and definitional of oligodendrogliomas, irrespective of cellular morphology. While many centers still assess 1p/19q copy number via fluorescence in situ hybridization (FISH), this methodology typically assesses only a small region of each chromosomal arm (ie, via a single probe on each arm). Very focal deletions may lead to false-positive results relative to the biologically relevant alteration that requires whole-arm loss of 1p and 19q resulting from an unbalanced translocation involving the opposite arms. Thus, the use of additional methods to interrogate each chromosomal arm more broadly (eg, via next-generation sequencing assays, single-nucleotide polymorphism arrays, or methylation array profiling) may be necessary when FISH results do not align with other information relevant to the case.

Oligodendrogliomas are further characterized by recurrent *TERT* promoter variations, although these are neither necessary nor sufficient for the diagnosis even in the context of IDH-mutated gliomas. *TERT* promoter variations interestingly characterize not only oligodendrogliomas, but also glioblastomas, and there is mutual exclusivity of *TERT* promoter variations with the ATRX variations that typify IDH-mutant astrocytomas.[16]

As is the case in IDH-mutant astrocytomas, the independent prognostic value of grade 2 versus 3 histologic criteria, if any, is not fully resolved in the modern diagnostic era. *CDKN2A* status, as in tumors diagnosed as *astrocytoma, IDH-mutant*, is also predictive of poor prognosis in the setting of oligodendrogliomas and imparts a grade of 3.

Glioblastoma, *IDH*-Wildtype

Glioblastomas remain the most malignant form of primary gliomas recognized in adults with a median survival time of 1 year in the absence of adjuvant therapy. Such therapy typically includes the alkylating agent temozolomide and radiation therapy, the standard Stupp protocol against which newer clinical trials are compared.[17] Current definitional criteria of glioblastomas, comprise a combination of histologic and molecular features with the prerequisite that the tumor is a diffuse astrocytic glioma lacking *IDH* variation, and that pediatric-type diffuse gliomas (see the section Pediatric-Type Diffuse Low-Grade Gliomas) have been excluded. To meet criteria for a glioblastoma the tumor must harbor at least one of the following: microvascular proliferation, necrosis, *TERT* promoter variation, *EGFR* amplification, or the combined presence of chromosome 7 gain and chromosome 10 loss. In practice, resected tumors often demonstrate all five of these features, although the implications of these criteria are better appreciated through less typical case examples (CASE 1-1). Indeed, a diagnosis of glioblastoma may be rendered with a single unstained slide containing only minimal core biopsy material with limited cellularity and lacking mitotic activity, microvascular proliferation, or necrosis if, for example, a FISH study reveals a subset of cells with convincing amplification of the *EGFR* locus.

The 2021 WHO CNS tumor classification retains explicit recognition of several histologic subtypes of glioblastomas including epithelioid glioblastomas, gliosarcomas, and giant cell glioblastomas.

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CASE 1-1

A 71-year-old woman with a history of multiply recurrent ovarian carcinoma presented with 2 weeks of feeling occasionally lightheaded. She was found unresponsive at home after a severe episode of lightheadedness, and subsequent MRI showed an expansile T2-weighted hyperintense, noncontrast enhancing lesion within the right mesial temporal lobe (FIGURE 1-1A). A biopsy demonstrated mildly hypercellular brain tissue suspicious for a glioma (FIGURE 1-1B). Given the nondiagnostic histology, the material was submitted for targeted panel sequencing, which showed polysomy for chromosome 7, monosomy of chromosome 10, and a truncating variation in *PTEN*. No variations in *IDH1/2* or *TERT* promoter were identified. Based on these findings, the decision was made to treat it as a glioblastoma. A completion resection was performed 5 weeks after the initial biopsy, and the histology at this time showed unequivocal features of a glioblastoma (FIGURE 1-1C). *MGMT* testing showed an absence of promoter methylation, and despite standard treatment with temozolomide and radiation, the patient died of the disease 17 months later.

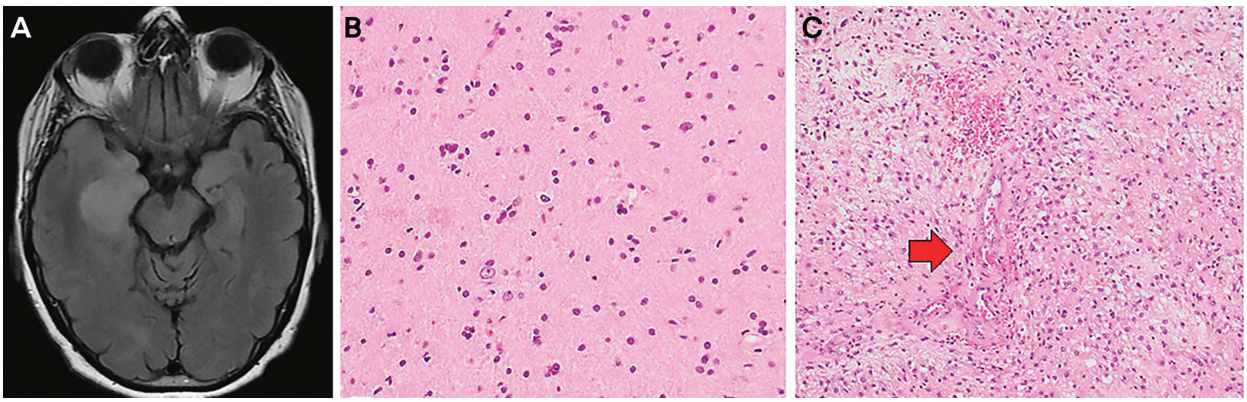

FIGURE 1-1
Imaging and histology of the patient in CASE 1-1. A, Axial fluid-attenuated inversion recovery (FLAIR) brain MRI showing an expansile right mesial temporal lesion. B, Representative photomicrograph of the biopsy showing minimally hypercellular white matter. C, Resection of the same lesion 5 weeks later showing classic histology of a glioblastoma, with densely cellular tumor and microvascular proliferation (arrow).

COMMENT

IDH-wildtype gliomas rarely present in older adults with low-grade imaging and histologic features; however, the presence of aggressive genomic alterations (in this case, gain of chromosome 7 and loss of chromosome 10) portends behavior tantamount to glioblastoma. This case illustrates how rapidly such tumors can evolve and demonstrates the power of integrating genomic testing for tumor grading, especially when histologic findings are subtle.

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Epithelioid glioblastomas, characterized by discohesive epithelioid, rhabdoid, or melanoma-like cells along with other features of glioblastomas, are enriched in *BRAF*^{V600E} variations, a targetable alteration, much like this subtype's morphological cousin, pleomorphic xanthoastrocytomas.[18]

Giant cell glioblastomas, characterized by frequent multinucleated tumor cells with expansive cytoplasm, show enrichment in *TP53* variations and frequent near-haploidy.[19] In addition, these tumors may demonstrate mismatch repair deficiencies and should be evaluated for mismatch repair–related proteins by performing immunohistochemistry for MLH1, MSH2, MSH6, and PMS2.

Gliosarcomas are biphasic tumors comprising glial fibrillary acidic protein (GFAP)-positive tumor cells as in classic glioblastomas along with areas with spindled cells, a sarcomatoid growth pattern, loss of GFAP expression, and deposition of intercellular collagen.

Finally, a glioblastoma harboring a poorly differentiated or so-called primitive neuronal component may demonstrate subclonal amplifications in *MYC* or *MYCN* and may disseminate broadly via the CSF.

PEDIATRIC-TYPE DIFFUSE HIGH-GRADE GLIOMAS

Gliomas arising in the pediatric population are characterized by unique molecular alterations that distinguish them from adult high-grade gliomas.

Diffuse Midline Glioma, H3 K27-Altered

In 2012, two groups concurrently reported that *H3F3A*, the gene encoding the histone protein H3.3, is recurrently altered in high-grade gliomas arising in children.[20,21] Interestingly, the same gene may harbor variants at two different codons in a way that is predictive of the anatomical location of the tumor, with recurrent K27 alterations seen in midline gliomas and codon G34 variations seen in cerebral hemispheric gliomas. For clarity, it should be noted that the current molecular nomenclature denotes the affected codons as K28 and G35, which become the 27th and 34th residues within the protein product only after the initial methionine is cleaved posttranslationally.

Diffuse midline gliomas with H3 K27 alterations are characterized by widespread loss of the epigenetically important trimethylation mark at lysine residue K27 of H3 histone proteins (H3K27me3), even in proteins derived from wildtype alleles of H3 genes within the same tumor cells. Loss of H3K27me3 can be demonstrated simply and cost-effectively by immunohistochemistry and is essential for the diagnosis of *diffuse midline glioma, H3 K27-altered*. While the most common alteration is a missense mutation of K28M (K27M), other alterations may lead to similar dysregulation of H3K27me3, including overexpression of EZHIP. Additional tumors in this family, including those presenting with bithalamic involvement, may also harbor *EGFR* alterations but retain the universal feature of H3K27me3 loss. In up to 20% of cases, instead of *H3F3A* variations mediating the H3.3 alteration, other genes encoding the protein isotype H3.1 with similar K27M variations may be encountered, including *HIST1H3B/C*. While tumors with H3.1 variations are similar in many respects, potentially clinically important distinctions exist including distinct commonly co-occurring variations and worse outcomes in H3.3 altered tumors.[22]

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Diffuse Hemispheric Glioma, H3 G34-Mutant

The same gene most commonly implicated in H3 K27-altered tumors, *H3F3A*, also harbors variants at a different site, G34 (or G35 if including the initial methionine residue that is cleaved during translation), in tumors arising in teenagers and young adults and within the cerebral hemispheres in contrast to midline locations. Most tumors additionally show both *TP53* and *ATRX* variations. Note that, as with K27-altered midline gliomas, even in the absence of histologic features historically regarded as high grade, such as microvascular proliferation and necrosis, a CNS WHO grade of 4 still applies as long as the requisite histone variation is demonstrated. Outcomes are poor with a typical survival time of 1.5 to 2 years.

Infant-Type Hemispheric Glioma

These recently described and rare tumors arise almost exclusively within the first year of life as large hemispheric masses that may involve the overlying leptomeninges. They are driven by fusion proteins involving one of several receptor tyrosine kinases including those encoded by *NTRK1/2/3, ROS1, ALK,* or *MET.*[23] Their histology may resemble that seen in classic glioblastomas. In addition to the identification of the relevant fusion driver, methylation array profiling may also be used to make this diagnosis.

PEDIATRIC-TYPE DIFFUSE LOW-GRADE GLIOMAS

Pediatric-type low-grade diffuse gliomas are molecularly distinct from their adult-type counterparts and do not exhibit *IDH* variations (by definition), although, as mentioned, on occasion adult-type *IDH*-mutated tumors may arise in younger patients. Instead, many pediatric low-grade gliomas are driven by oncogenic fusion events. These include fusions involving the *MYB* and *MYBL1* genes, which when detected are incorporated in the diagnostic name (eg, *diffuse astrocytoma, MYB-altered*). These tumors frequently present in the temporal lobe of patients with epilepsy. In some cases, there is an angiocentric arrangement of tumor cells and when this is particularly prominent, often in cases with *MYB-QKI* fusion, the tumor may be designated as an angiocentric glioma, a tumor with a methylation profile that overlaps with other *MYB*-altered tumors. *MYB*-altered tumors are designated as CNS WHO grade 1, and available data suggests better outcomes in these patients.[24]

Some tumors with a diffusely infiltrative pattern in fact harbor $BRAF^{V600E}$ mutations, an alteration more commonly encountered in nondiffuse tumors including pleomorphic xanthoastrocytomas, gangliogliomas, and a subset of pilocytic astrocytomas. Other mitogen-activated protein kinase (MAPK) alterations besides those in *BRAF* may be encountered and the WHO considers this group of tumors as *diffuse pediatric-type glioma, MAPK-altered.* The presence of $BRAF^{V600E}$ variations in such a wide range of tumors, including multiple fundamentally astrocytic tumors, highlights the fact that histologic and radiologic assessment (or methylation profiling) is still necessary to determine whether a tumor should be regarded fundamentally as "diffuse" or circumscribed.

Finally, an entity known as polymorphous neuroepithelial tumor of the young has gained increasing recognition since its initial description in 2017.[25] Another diffuse glioma arising typically in younger patients with epilepsy, these tumors feature oligodendroglioma-like neoplastic components and are characterized by

KEY POINTS

- **Tumors lacking *IDH1/2* variations frequently show gain of chromosome 7, loss of chromosome 10, *TERT* promoter variation, or *EGFR* amplification. These features can also be used to diagnose glioblastomas in the absence of classic histology.**
- **Gliomas with histone H3 variations comprise a subset of highly aggressive tumors that occur in children and young adults. Diffuse midline gliomas carry variations or epigenetic dysregulation at K27, while diffuse hemispheric gliomas carry G34 variations.**

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diffuse, strong immunohistochemical labeling for CD34, a feature that readily suggests this diagnosis even prior to receipt of molecular testing. Most examples of polymorphous neuroepithelial tumor of the young harbor either the common *BRAF*^{V600E} alteration or are driven by *FGFR2/3* fusion events. Like other pediatric diffuse low-grade gliomas, outcomes are generally favorable following surgical resection, and the tumor is assigned CNS WHO grade 1,[25] with the caveat that the full spectrum of tumors that may be regarded as polymorphous neuroepithelial tumor of the young remains to be fully determined and rare examples of malignant progression have been reported.[26]

CIRCUMSCRIBED GLIOMAS

In contrast to diffuse gliomas, which show ill-defined borders and crawl along axons and blood vessels, circumscribed gliomas form sharp borders with surrounding brain tissue and do not exhibit significant microscopic invasion of adjacent structures.

Pilocytic Astrocytoma

Pilocytic astrocytomas are the most common gliomas in children, accounting for nearly 20% of all childhood brain tumors. Tumors most often occur in the cerebellum and optic nerve, but they may also arise in other midline locations such as the brainstem, deep nuclei, and hypothalamus. The histologic spectrum of pilocytic astrocytomas is broad, but common findings include paucicellular tumors composed of hairlike pilocytes, oligodendroglioma-like cells, or both, a biphasic combination of compact regions with Rosenthal fibers and looser myxoid regions, and abnormal vasculature. The most stereotypic molecular alteration in pilocytic astrocytomas is a 3′ duplication of the kinase region of *BRAF*, leading to a *KIAA1549::BRAF* fusion product. *NF1* loss-of-function events are also common, more so in tumors involving the optic pathway. Many other MAPK pathway-activating events have been described, including hotspot mutations in *BRAF*, *FGFR1*, and *KRAS*, and fusions involving *FGFR1* and the NTRK family of genes.[27,28] Pilocytic astrocytomas rarely reoccur after complete resection and are assigned CNS WHO grade 1.

High-Grade Astrocytoma with Piloid Features

High-grade astrocytomas with piloid features are a newly added entity with a distinct methylation signature that includes tumors showing histology overlapping with both pilocytic astrocytomas and glioblastomas. These rare tumors have mostly been described in adults and typically arise within the cerebellum.[29] Genetically, they are characterized by activating events in the MAPK pathway along with *CDKN2A/B* deletions and frequent loss-of-function alterations in *ATRX*. Prognosis is similar to that of grade 4 *IDH*-mutant astrocytomas based on thus far limited follow-up studies.[29]

Pleomorphic Xanthoastrocytoma

Pleomorphic xanthoastrocytomas are astrocytic gliomas with highly characteristic histologic features (eg, bizarre nuclear pleomorphism, lipidized cells, eosinophilic granular bodies) that frequently arise within the superficial cerebrum, especially in the temporal lobe of children and young adults. Tumors most often possess *BRAF* p.V600E variations and *CDKN2A/B* deletions; however, other MAPK pathway-activating alterations have also been reported.[30]

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Pleomorphic xanthoastrocytomas are prone to reoccur and undergo malignant progression and may be assigned CNS WHO grade 2 or 3 on the basis of mitotic activity.

Subependymal Giant Cell Astrocytoma

Subependymal giant cell astrocytomas are low-grade astrocytic tumors arising within subependymal tissue typically in the lateral ventricles that are strongly associated with tuberous sclerosis. Although they are considered CNS WHO grade 1, larger lesions may cause significant morbidity.

Chordoid Glioma

Chordoid gliomas are extremely rare tumors most often located in the anterior region of the third ventricle, and carry a highly recurrent p.D463H variation in *PRKCA*.[31,32] Given the sensitive anatomic location of these tumors, they are considered CNS WHO grade 2.

Astroblastoma, *MN1*-Altered

Astroblastomas are rare glial neoplasms that typically arise in the cerebral hemispheres of female children and young adults. The histologic features of these entities are extremely varied and overlap with several different gliomas, embryonal tumors, and ependymal neoplasms. Nonetheless, they are characterized by recurrent fusion events involving *MN1*, often with *BEND2* as its partner.[33] Outcome data are limited given the rarity of these tumors; however, high survival rates have been noted.[34,35]

GLIONEURONAL AND NEURONAL TUMORS

Tumors showing microscopic evidence of neuronal differentiation are in general very well differentiated and indolent in behavior. Most demonstrate simplistic genomic profiles with single, characteristic driver events.

Gangliocytoma

Gangliocytomas are rare epileptogenic tumors composed entirely of neoplastic ganglion cells that are most often seen in childhood. Although they may arise throughout the neuraxis, those associated with Cowden syndrome (dysplastic cerebellar gangliocytomas or Lhermitte-Duclos disease) exclusively occur in the cerebellum. Diagnostic genetic alterations and profiles have not thus far been identified in sporadic cases.

Ganglioglioma

Gangliogliomas are biphasic tumors composed of both mature neoplastic ganglion cells and glial cells that are most frequently encountered in the temporal lobe of children, although tumors may be seen in a wide range of patient ages and anatomic locations. Imaging studies typically show mixed solid and cystic lesions with variable contrast enhancement. Alterations in the MAPK signaling pathway are characteristic of this tumor, with the majority being *BRAF* p.V600E alterations.[36,37] Tumors are usually indolent and correspond to CNS WHO grade 1.

Desmoplastic Infantile Ganglioglioma and Astrocytoma

Desmoplastic infantile gangliogliomas and desmoplastic infantile astrocytomas are highly related benign tumors showing either mixed glial and neuronal

KEY POINTS

- **Pediatric low-grade diffuse gliomas often exhibit morphologic overlap with adult gliomas; however, they are much more indolent and contain unique driver mechanisms that often activate the MAPK pathway.**
- **Fusions involving *BRAF*, especially with the fusion partner *KIAA1549*, are highly characteristic of pilocytic astrocytomas. Alterations have also been described in other genes (eg, *NF1*, *FGFR1*, *BRAF*).**

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features or purely glial morphology, respectively. These tumors characteristically occur as large superficial cystic lesions in the cerebral hemispheres of children under 2 years old. Recurrent activating variations in the MAPK pathway have been described, mostly within *BRAF*.[38] Most tumors do not reoccur when complete surgical resection is feasible, and malignant transformation is exceedingly rare.

Dysembryoplastic Neuroepithelial Tumor

Dysembryoplastic neuroepithelial tumors are another type of benign epileptogenic tumor that present in the first two decades with medically refractory epilepsy. Tumors are usually cortically based and arise preferentially within the temporal lobe. Activating hotspot variations or internal tandem duplications of the kinase domain of *FGFR1* are most common in dysembryoplastic neuroepithelial tumors.[39]

Other Glioneuronal Tumors

Several additional rare glioneuronal tumors are included in the 5th edition of the CNS WHO classification of tumors, which can show overlapping features and often require molecular testing for confirmation. All of the following tumors are CNS WHO grade 1, and key differentiating features are highlighted. Papillary glioneuronal tumors are usually supratentorial and periventricular in location, and the diagnostic genetic event is *PRKCA* gene fusion.[40] Rosette-forming glioneuronal tumors arise in midline locations and prototypically exhibit *FGFR1* hotspot variations along with *PIK3CA* alterations, *NF1* alterations, or both.[41,42] Myxoid glioneuronal tumors harbor *PDGFRA* variations at p.K385 and most often involve the septum pellucidum and adjacent structures.[43] As the name implies, diffuse leptomeningeal glioneuronal tumors grow preferentially and extensively within the leptomeninges. Diagnostic molecular features include gain of chromosome arm 1q and *KIAA1549::BRAF* fusion, although other MAPK drivers may be found.[44] Multinodular and vacuolating tumors are epileptogenic hamartomatous lesions characterized by frequent *MAP2K1* alterations.[45] Lastly, diffuse glioneuronal tumors with oligodendroglioma-like features and nuclear clusters are rare tumors that to date can be recognized only by their distinct methylation profile.

Neuronal Tumors

Central neurocytomas are characteristically located within the lateral ventricles and show a tendency to reoccur despite their low-grade histologic appearance and are considered as WHO grade 2. Cerebellar liponeurocytomas are related entities that preferentially arise within the cerebellar hemispheres and exhibit a unique and defining adipocytic component. No defining genetic drivers have been identified thus far for these tumors. Despite their name, extraventricular neurocytomas are unrelated to the above tumors and show frequent *FGFR1* alterations, specifically *FGFR1::TACC1* fusions.[46] They also carry a WHO grade 2 designation.

CRANIOPHARYNGIOMAS

Craniopharyngiomas are squamous epithelial tumors that arise within the sellar and infundibulotuberal regions of children and adults. Adamantinomatous craniopharyngiomas are the most common subtype, which are characterized by

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keratin production, calcification, and recurrent activating variations in exon 3 of *CTNNB1*.[47] By contrast, papillary craniopharyngiomas lack keratin production, occur predominantly in adults, and harbor activating *BRAF* p.V600E variations,[48] which render them particularly sensitive to targeted inhibition.[49,50] In general, survival rates are high when gross total resection is feasible for these tumors.

EPENDYMOMAS

Ependymal tumors have undergone extensive reorganization in recent years and are now subclassified on a combination of histologic, molecular, and anatomic characteristics. Within the supratentorial compartment, recurrent fusion events in *ZFTA* or *YAP1* identify two new subgroups, which largely occur in children and show distinct outcomes.[51] Posterior fossa tumors fall primarily within two molecular subgroups: posterior fossa A or B. The posterior fossa A subgroup is highly aggressive and characterized by recurrent gains of chromosome 1q, but relatively few other genomic changes. The posterior fossa B subgroup, by contrast, usually shows numerous whole-chromosome gains and losses and is significantly more indolent.[51] Both posterior fossa subgroups are reliably subclassified by methylation analysis, which is the currently preferred modality of testing. Not only does methylation array profiling generate subgroup information independent of copy number alterations, but the same test can additionally yield a copy number profile for further assessment of 1q and other arm-level gains or losses. In practice, immunohistochemical staining for the histone methylation mark H3K27me3 can act as a quick and reliable surrogate for posterior fossa A versus B subtyping where loss of H3K27me3 labeling in tumor cells shows strong a correlation with the posterior fossa A subtype. Spinal ependymomas of conventional histology typically harbor *NF2* alterations, while those containing *MYCN* amplifications carry a much worse prognosis.[52] Myxopapillary ependymomas characteristically occur near the conus medullaris, and their genomic profile is similar to that of the posterior fossa B subgroup.[51] Subependymomas may occur in all three anatomic compartments and remain largely a histologic diagnosis with CNS WHO grade 1 behavior.

Grading of ependymomas on histologic grounds continues to be of questionable utility, as molecular profiling has proved more accurate at identifying tumors with significantly poorer outcomes.[53] Grade 2 or 3 may still be applied to conventional ependymomas as deemed appropriate; however, the term *anaplastic ependymoma* as well as other histologic subtypes (eg, tanycytic, clear cell, papillary) are no longer used. Additionally, myxopapillary ependymomas are now listed as being grade 2, given their high propensity to reoccur.

EMBRYONAL TUMORS

Embryonal tumors are highly aggressive, poorly differentiated malignancies that frequently pose diagnostic challenges given their highly overlapping appearances. Most require comprehensive molecular testing for accurate classification.

Medulloblastoma

Medulloblastomas derive from cerebellar precursors and are one of the most common childhood CNS tumors. They are subclassified based on both histologic

KEY POINTS

- Circumscribed gliomas are highly variable in behavior, ranging from benign (subependymal giant cell astrocytomas), to intermediate malignancy (chordoid gliomas, pleomorphic xanthoastrocytomas, astroblastomas), to highly aggressive (high-grade astrocytomas with piloid features).
- Similar to other pediatric low-grade gliomas, glioneuronal tumors exhibit a wide range of histologies and possess driver events, most commonly in the MAPK pathway.
- Ependymoma classification is based largely on the anatomic compartment (supratentorial, posterior fossa, and spine) and genetic and epigenetic profiles. While histologic grading is of limited utility, the posterior fossa A and *MYCN*-amplified spinal tumors are particularly aggressive.
- Molecular subclassification of medulloblastomas is paramount for prognosis and treatment planning. While wingless and INT-1 (WNT)-activated and sonic hedgehog (SHH)-activated groups can be classified with most next-generation sequencing panels, groups 3 and 4 (non-WNT, non-SHH) frequently require methylation profiling for accurate diagnosis.

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appearance and molecular profile; however, with the exception of desmoplastic and nodular morphology, other microscopic patterns do not correlate well with molecular classes. Current practice dictates assigning molecular subclasses when possible, which include wingless and INT-1 (WNT)-activated, sonic hedgehog (SHH)-activated (*TP53*-wildtype or *TP53*-mutant), and non-WNT/non-SHH (groups 3 and 4).[54]

WNT-activated medulloblastomas arise in the dorsal brainstem in older children and young adults, usually harboring exon 3 activating variations in *CTNNB1* or less commonly in *APC*, the latter of which may be encountered in Turcot syndrome.[55] Immunohistochemistry for β-catenin often shows nuclear positivity, although the focality and variability of staining usually require molecular confirmation. WNT-activated medulloblastomas have an excellent prognosis with standard therapy, with a 5-year survival rate of more than 90% and high cure rates.

SHH-activated medulloblastomas occur in the cerebellar hemispheres with a bimodal age distribution in young children and young adults. SHH-activated *TP53*-wildtype medulloblastomas generally have a good prognosis. Inactivating variations in *PTCH1* are the most frequent mechanism of SHH upregulation, whereas variations in *SUFU* or *SMO* can be seen more often in adults (CASE 1-2).[56]

TP53-mutant tumors occur in older children and young adults and have a much worse prognosis. Gene amplification events, such as in *GLI2* or *MYCN*, are more common in this subset of SHH-activated medulloblastomas than the gene variation events above.[57]

Group 3 medulloblastomas (non-WNT and non-SHH activated) are the most aggressive subclass and occur most often in young children. Amplification of *MYC* is associated with this subclass; however, occurrence is infrequent. Few other readily testable genomic events define group 3 tumors, which generally require methylation analysis for assignment.

The majority of medulloblastomas fall into group 4 (also non-WNT/non-SHH activated) and are typically seen in older children and adolescents with a 3:1 male-to-female ratio. The prognosis is favorable with standard therapy, and like group 3 tumors they require methylation analysis for definitive classification.[58]

Atypical Teratoid/Rhabdoid Tumor

Atypical teratoid/rhabdoid tumors are CNS extrarenal malignant rhabdoid tumors encountered predominantly in children younger than 2 years old. Tumors may arise throughout the neuraxis, with frequent leptomeningeal spread at presentation.[59] The histologic appearance of atypical teratoid/rhabdoid tumors is highly variable, usually showing primitive tumor cells with at least focal regions of rhabdoid morphology. Loss of INI1 expression or, rarely, of BRG1 expression is required for the diagnosis, corresponding to biallelic inactivation of *SMARCB1* or *SMARCA4*. Recent studies have identified three distinct transcriptional and epigenetic subgroups of atypical teratoid/rhabdoid tumors, which show slightly different clinicopathologic features. The subgroups were assigned the terms "TYR," "SHH," and "MYC" to reflect the upregulation of genes related to melanogenesis (including the *TYR* gene encoding tyrosinase), the SHH pathway, and upregulation of the *MYC* gene itself, respectively.[60] Atypical teratoid/rhabdoid tumor-TYR characteristically arises in the infratentorial region in infants, expresses melanocytic markers such as tyrosinase, and may have better

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survival outcomes.[61] Atypical teratoid/rhabdoid tumor-MYC occurs supratentorially in older children, and atypical teratoid/rhabdoid tumor-SHH has been described throughout the neuraxis and characteristically harbors activating mutations in SHH and NOTCH gene pathways. Atypical teratoid/rhabdoid tumors carry a nearly uniformly dismal prognosis with rare instances of long-term survival, and further study is needed to assess the value of routine molecular subtyping.

Embryonal Tumor with Multilayered Rosettes, C19MC-Altered

Embryonal tumors with multilayered rosettes are highly aggressive primitive tumors that usually occur in the supratentorial compartment in children under 2 years old. They are defined by the amplification of a microRNA cluster on chromosome 19 (C19MC), which usually results in the rearrangement of *TTYH*.[62] Prior to the unification of this entity with molecular profiling, three distinct histologic patterns were described (embryonal tumor with abundant neuropil and true rosettes, ependymoblastoma, and medulloblastoma), all of which show primitive poorly differentiated tumor cells arranged in multilayered rosettes. The prognosis of embryonal tumors with multilayered rosettes is uniformly poor irrespective of growth pattern, with an average survival time of less than 1 year.[63,64]

CNS Neuroblastoma, *FOXR2*-Activated

CNS neuroblastoma, *FOXR2*-activated was discovered through large cohort methylation analysis of embryonal tumors when recurrent *FOXR2* rearrangements were identified in tumors resembling extra-CNS neuroblastomas.[33] Tumors typically arise in the cerebral hemispheres or subventricular locations, and the prognosis is not well characterized. *FOXR2* alterations are generally not covered by most existing next-generation sequencing methods, necessitating methylation analysis for confirmation.

CNS Tumor with *BCOR* Internal Tandem Duplication

CNS tumors with *BCOR* internal tandem duplication are another type of CNS embryonal tumor identified by their distinct methylation profile. Tumors universally harbor short internal tandem duplications within the terminal exon of *BCOR*. Occurrence within the cerebral and cerebellar hemispheres is most frequent, and they may appear well demarcated from surrounding brain parenchyma. The immunophenotype is nonspecific, and confirmation of the diagnosis requires next-generation sequencing or methylation testing. Although outcome data are limited, most tumors show aggressive behavior and rapid progression.[65]

TUMORS OF MESENCHYMAL ORIGIN

Outside of meningiomas, few mesenchymal neoplasms arise uniquely within the neuraxis. As a result, this section focuses on special grading considerations and diagnostic molecular findings for CNS tumors where appropriate.

Meningioma

Meningiomas comprise the largest and most common mesenchymal tumor class arising within the CNS. These neoplasms may arise throughout the neuraxis; however, the majority occur intracranially within the convexity and skull base. These tumors are most frequent in adult women, with a peak incidence in the

KEY POINTS

- Although atypical teratoid/rhabdoid tumors can be easily diagnosed by light microscopy, three distinct transcriptional and methylation subgroups have been identified that may show distinct survival outcomes.
- Embryonal tumors with multilayered rosettes possess highly characteristic amplifications of a microRNA cluster on chromosome 19 (C19MC) that can only be detected by whole-genome array or next-generation sequencing platforms (including methylation arrays).
- Other recently described embryonal tumors such as CNS neuroblastomas or CNS tumors with *BCOR* internal tandem duplication may need methylation profiling to classify, given the lack of adequate coverage of their diagnostic genetic events on most available next-generation sequencing platforms.

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fifth and sixth decades.[66] The vast majority of these tumors are slow-growing and indolent in behavior, corresponding to WHO grade 1. When present, clinical symptoms are usually insidious in onset and related to compression of underlying structures. The risk of local recurrence is approximately 20% at 20 years, and surgical resection is often sufficient for long-term control.[67] A small subset of tumors shows an increased risk of recurrence or frankly malignant behavior and may be designated as WHO grade 2 or 3, respectively, on the basis of various histologic and molecular features discussed below.

CASE 1-2

A 3-year-old boy presented with severe headache and vomiting. MRI of the brain demonstrated a 4.7-cm cerebellar mass centered within the vermis causing obstructive hydrocephalus, with mass effect on the fourth ventricle (FIGURE 1-2A). MRI of the brain and spine showed no evidence of leptomeningeal dissemination. Pathology showed a hypercellular small blue cell tumor with nodules of better-differentiated cells (FIGURE 1-2B and 1-2C). Reticulin staining showed collagen deposition (desmoplasia) in the internodular zones (FIGURE 1-2D), while Ki67 showed reduced labeling within the nodules (FIGURE 1-2E). A diagnosis of desmoplastic nodular medulloblastoma was rendered. The immunophenotype was consistent with the sonic hedgehog (SHH)-activated molecular subtype. The tumor was wildtype for *TP53* both by immunohistochemical and molecular assessment. Sequencing studies revealed a germline *PTCH1* variation, consistent with Gorlin syndrome. Following surgical resection and chemotherapy, the patient had a recurrence within 1 year, which was again treated with chemotherapy. The patient has since had stable disease.

COMMENT

The diagnostic assessment of medulloblastomas requires both histologic and molecular subtyping. While there is a strong correlation between the desmoplastic nodular variant and SHH-activated tumors, other histologic subtypes, such as the classic variant, may show a range of molecular subtypes. In addition to oncogenic drivers of disease for the tumor in question, sequencing studies may also demonstrate underlying germline alterations, as in this patient, that are important to recognize for overall patient management and follow-up.

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Grading of meningiomas is performed via histologic assessment of several criteria, including tumor mitotic rate, brain invasion, and tumor necrosis, growth pattern, cellular density, and nuclear appearance. Myriad histologic subtypes of meningiomas have been described, many of which have been shown to correlate strongly with clinical behavior and possess unique genomic profiles. Secretory meningiomas are universally benign, frequently encountered on the skull base, and show characteristic variations in *KFL4* and *TRAF7*.[68] Angiomatous or microcystic meningiomas are also most often grade 1, and a large proportion of

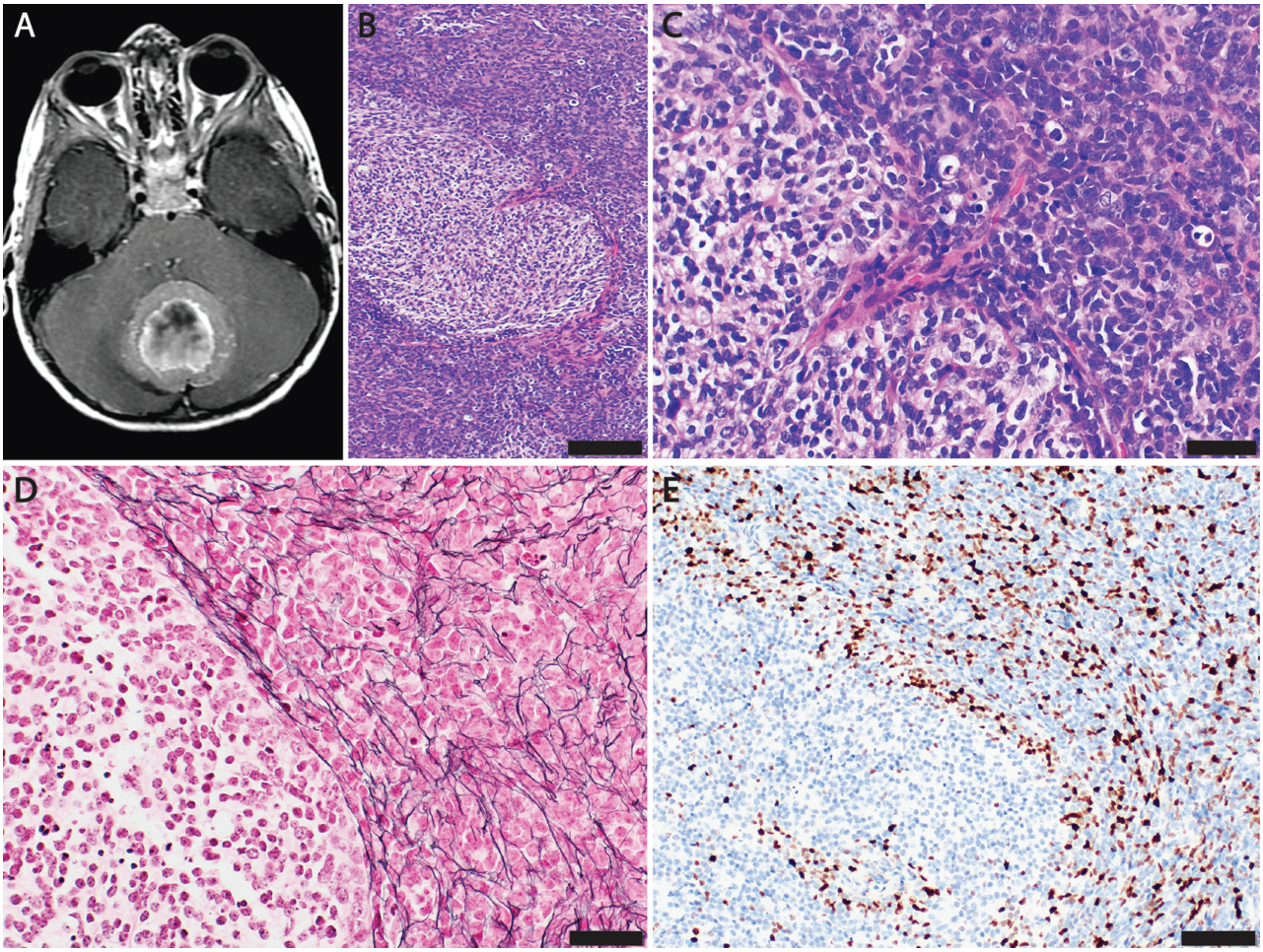

FIGURE 1-2
Imaging and histology of the patient in CASE 1-2. Axial T1-weighted postcontrast MRI shows a heterogeneously enhancing mass centered within the cerebellar vermis (*A*). A low-power hematoxylin and eosin (H&E)-stained section shows a pattern of sheets of small blue cells interrupted by nodules of relative hypocellularity (*B*). A high-power H&E-stained section at the interface of a nodule again shows the biphasic nature of the desmoplastic nodular variant (*C*) with the more primitive component (*C*, *upper right*) highlighted by reticulin staining (*D*) that shows interwoven collagen fibrils. Ki67 (MIB-1) labeling shows relatively lower proliferative activity in the better-differentiated nodules (*E*, *lower left*). Scale bars: *B*: 200 μm; *C* and *D*: 50 μm; *E*: 100 μm.

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this subtype shows recurrent whole-chromosome gains,[69] which is not seen among other meningioma subtypes. Chordoid and clear cell meningiomas are classified as WHO grade 2, irrespective of the presence or absence of conventional histologic grading criteria. Of these, clear cell meningiomas characteristically show *SMARCE1* inactivation and may present as familial spinal tumors.[70,71] Papillary and rhabdoid morphologic subtypes are definitionally WHO grade 3. A subset of rhabdoid meningiomas is associated with *BAP1* predisposition syndrome, showing loss of BAP1 expression.[72]

Tumors with fibroblastic, meningothelial, or transitional histologies are most common and span all WHO grades (1-3). *NF2* inactivation is the most frequent genetic finding in these tumors and is thought to drive tumorigenesis. Higher-grade meningiomas show a stereotyped series of chromosomal changes, leading to the proposal of several new integrated grading schemas, analogous to what is currently employed in diffuse gliomas.[6,73,74] Grade 2 meningiomas show highly recurrent chromosomal losses, of which 1p loss has been demonstrated repeatedly to carry independent prognostic value. In addition to these changes, grade 3 tumors show frequent homozygous deletion of *CDKN2A/B* and *TERT* promoter variations. The presence of either or both of these events strongly correlates with grade 3 behavior and formal assignment of WHO grade 3 may now be made in the absence of convincing histologic features.[1] Although not yet employed clinically, distinct methylation subclasses of meningiomas have been described, which also show promising predictive value.[6,73]

Solitary Fibrous Tumor

Formerly known as *hemangiopericytoma*, meningeal solitary fibrous tumors are dural-based fibroblastic neoplasms with clinical features that overlap with meningiomas. Like solitary fibrous tumors of the periphery, meningeal solitary fibrous tumors are characterized by *NAB2::STAT6* gene fusion.[75] Meningeal solitary fibrous tumors frequently reoccur locally, and distant metastases may present many years after initial diagnosis. Like meningiomas, solitary fibrous tumors may be classified as WHO grade 1-3 on the basis of mitotic rate and the presence or absence of necrosis. Additional molecular alterations such as *TERT* promoter and *TP53* variations have been associated with more aggressive behavior, but these events are not currently assayed in routine clinical evaluation.[76,77]

Vascular Lesions

Cerebral arteriovenous malformations are congenital vascular anomalies composed of malformed vessels exhibiting both arterial and venous histologic features with intervening brain parenchyma. Given their fragile vasculature, arteriovenous malformations carry a 2% to 5% risk of hemorrhage per year and a significant risk of death upon rupture.[78] Cavernous malformations by contrast have no arterial or venous features and no intervening brain tissue. Although many are sporadic or arise following radiation therapy, familial forms exist and are associated with germline variations in *KRIT*, *CCM2*, and *PDCD10*.[79] Hemangiomas of the CNS are benign vascular neoplasms composed of various-sized vessels that may arise spontaneously or in association with PIK3CA-related overgrowth syndrome. In adults, hemangiomas typically occur in vertebral bodies or the frontal skull. Hemangioblastomas are another type of benign vascular tumor characteristically located in the cerebellum of adults, and

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imaging typically demonstrates contrast-enhancing cystic lesions with mural nodules. Hemangioblastomas are driven by alterations in *VHL* and may occur either sporadically or in the setting of von Hippel-Lindau syndrome.[80]

Chondroid, Osseous, and Notochord Lesions

Many bone and soft tissue neoplasms that commonly arise outside of the CNS, such as fibrous dysplasias, chondrosarcomas, osteosarcomas, rhabdomyosarcomas, Ewing sarcomas, mesenchymal chondrosarcomas, chordomas, and peripheral nerve sheath neoplasms, may present intracranially and will not be discussed further in this article.

Tumors of Uncertain Differentiation

Three new mesenchymal histomolecular entities were introduced in the 5th edition of the WHO classification of CNS tumors. While all are very rare and their clinicopathologic features are still being described, it is important to recognize how they differ from more common CNS tumors.

Intracranial mesenchymal tumor, FET-CREB fusion-positive is a histologically diverse neoplasm characterized by the fusion of a FET family member, most often *EWSR1*, with a member of the CREB family (*CREB1*, *ATF1,* or *CREM*). These tumors tend to present as extra-axial masses in the supratentorial compartment in children and young adults. The microscopic appearances occasionally correlate with a gene-fusion product, and the immunohistochemical profile (occasional EMA positivity) may overlap with meningiomas. Given this variable morphology and nonspecific molecular profile, the demonstration of a *FET::CREB* gene fusion must be integrated with the appropriate clinical and histologic setting to establish the proper diagnosis. The behavior of these tumors is unclear given the small number of described cases and varies from indolent to rapid recurrence.[81,82]

Primary intracranial sarcoma, *DICER1*-mutant is another diverse entity that encompasses histologies such as gliosarcomas, glioblastomas, mesenchymal chondrosarcomas, rhabdomyosarcomas, and primitive neuroectodermal tumors, unified by their methylation pattern and *DICER1*-inactivating variations.[83] These tumors have been described in both adults and children, where they may occur sporadically or in the setting of both *DICER1* syndrome and neurofibromatosis type 1.[84] Although these tumors likely follow an aggressive clinical course, more data are required to determine their natural history.

CIC-rearranged sarcomas are high-grade round cell mesenchymal neoplasms more often arising in younger patients outside of the CNS but may rarely occur within the brain as well. These sarcomas possess a characteristic fusion of *CIC* with various partners, such as *DUX4* (more common outside the CNS) or *NUTM1/2* (more common inside the CNS).[33,85] In addition to detecting the diagnostic fusion event, immunoreactivity for ETV4, WT1, and CD99 may be used to confirm the diagnosis. Outcomes of CNS *CIC*-rearranged sarcomas are not well described; however, initial reports as well as literature from extra-CNS tumors suggest an aggressive course and poor response to therapy.

KEY POINTS

- Despite long-established grading criteria for meningiomas, integration with cytogenetic and gene-variation data has shown significant improvement in predicting long-term behavior.
- Solitary fibrous tumors arising in the meninges are graded differently from non-CNS counterparts, considering only mitotic rate and the presence or absence of necrosis.
- Several new mesenchymal entities are recognized in the current WHO CNS tumor classification, including tumors with ***FET::CREB*** fusions, ***DICER1*** loss-of-function variations, and ***CIC*** rearrangements. While some are likely very aggressive, more data are needed to determine a precise WHO grade.

CONCLUSION

The diagnosis of brain tumors has shifted dramatically from strict reliance upon traditional light microscopy to pervasive integration with both genomic and

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epigenomic profiling, evidenced by the vast number of histomolecular entities in the 5th edition of the WHO classification of CNS tumors. In addition, several tumor types have incorporated genomic criteria within their grading schema, allowing for a more accurate assessment of prognosis, especially when biopsy samples are not representative. Lastly, proper triage of samples for ancillary testing has gained immense importance in the current environment, necessitating discussions of the powers and limitations of different testing modalities.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Adult-type Diffuse Gliomas

By Macarena I. de la Fuente, MD

ABSTRACT

OBJECTIVE: **This article highlights key aspects of the diagnosis and management of adult-type diffuse gliomas, including glioblastomas and *IDH*-mutant gliomas relevant to the daily practice of the general neurologist.**

LATEST DEVELOPMENTS: **The advances in molecular characterization of gliomas have translated into more accurate prognostication and tumor classification. Gliomas previously categorized by histological appearance solely as astrocytomas or oligodendrogliomas are now also defined by molecular features. Furthermore, ongoing clinical trials have incorporated these advances to tailor more effective treatments for specific glioma subtypes.**

ESSENTIAL POINTS: **Despite recent insights into the molecular aspects of gliomas, these tumors remain incurable. Care for patients with these complex tumors requires a multidisciplinary team in which the general neurologist has an important role. Efforts focus on translating the latest data into more effective therapies that can prolong survival.**

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr de la Fuente discusses the unlabeled/investigational use of vorasidenib in clinical trials for the treatment of brain tumors.

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INTRODUCTION

Gliomas are the most common malignant primary brain tumors in adults, with an average annual age-adjusted incidence rate of 5 per 100,000 population.[1,2] Although these tumors are relatively uncommon compared with brain metastases or benign primary brain tumors such as meningiomas, gliomas are associated with significant morbidity and mortality from both the tumor and treatment-related toxicities compared with other solid tumors.

Over the past 15 years, significant advances have been made in characterizing these tumors by identifying their molecular features. Louis and colleagues[3] summarize *Central Nervous System Tumours, WHO Classification of Tumours*, fifth edition, volume 6, which presents these characterizations. Adult-type diffuse gliomas are grouped into three entities: (1) *IDH*-wildtype glioblastomas, (2) *IDH*-mutant astrocytomas, and (3) *IDH*-mutant and 1p/19q-codeleted oligodendrogliomas.[4-6] Along with histologic features, this classification is based on the presence or absence of *IDH1* and *IDH2* gene variations, codeletion of chromosomal arms 1p and 19q, and a few other molecular alterations. For more information on these classifications, refer to the article "2021 World Health Organization Classifications of Brain Tumors," by David M. Meredith, MD, PhD and David J. Pisapia, MD, in this issue of *Continuum*.

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Despite the remarkable progress in tumor characterization and classification, there has been little advancement in survival-prolonging treatment for patients with these tumors, except for certain tumor subtypes. The care of patients with these complex tumors requires a multidisciplinary team, including neuro-oncologists, neurosurgeons, radiation oncologists, epileptologists, general neurologists, onco-psychiatrists, and other providers.

The aim of this article is to provide an update including clinical presentation, diagnosis, and management of patients with gliomas focusing on the most relevant data for the general neurologist.

KEY POINTS

- Gliomas are relatively uncommon but are associated with significant morbidity and mortality.
- For certain glial tumor subtypes, targeted therapies have emerged as promising treatment options.
- Researchers have made progress in understanding and classifying gliomas, but there has been limited progress toward prolonging patient survival.
- Glioblastomas are one of the most aggressive solid tumors and the most common malignant primary central nervous system tumors.
- Therapeutic ionizing radiation is the only well-established risk factor for the development of glioblastomas.
- The clinical presentation of glioblastomas depends largely on tumor location and can include elevated intracranial pressure symptoms and seizures.

GLIOBLASTOMAS

Malignant primary brain tumors cause more than 15,000 deaths per year in the United States. Glioblastomas are the most common malignant primary brain tumors.[1]

Overview and Epidemiology

Adult glioblastomas are one of the most deadly and aggressive of all malignant solid tumors,[1] and they are the most commonly occurring malignant primary central nervous system (CNS) tumors, representing 49.1% of malignant primary tumors and 14.3% of all primary CNS tumors.[1] The peak age-adjusted incidence of glioblastomas is 3.23 per 100,000 population per year. Glioblastomas are more common in males (1.6 times more common than in females) and more common among White people when compared with Hispanic White people, Black people, American Indians or Alaska Natives, and Asian people or Pacific Islanders.[2] The median age at diagnosis is 65 years. The incidence of glioblastomas increases with age, with rates highest in individuals aged 75 to 84 years.[1,2] The median overall survival time is 15 to 18 months, and the 5-year survival rate is 6.8%.[8-10]

In most cases, the etiology of glioblastomas is unknown. Researchers have investigated a variety of potential risk factors, including cell phones, electromagnetic radiation, and viral triggers; however, therapeutic ionizing radiation is the only well-established risk factor. Identified protective factors include atopic conditions (eg, asthma, eczema, hay fever, allergies), reducing the risk of gliomas by approximately 30%, and long-term use of low-dose aspirin.[11-13] Less than 5% of patients with glioblastoma have a germline alteration causing well-defined hereditary cancer syndromes, including Li-Fraumeni syndrome, familial adenomatous polyposis, Lynch syndrome, and neurofibromatosis type 1.[14] Given the low incidence of gliomas, germline testing is not standard practice.

Diagnosis

The clinical presentation of glioblastomas depends largely on tumor location. Hemiparesis, aphasia, sensory loss, or visual field disturbances are all common symptoms, as well as gait imbalance and urinary incontinence. Behavioral and neurocognitive changes are frequent, especially in older adults, and elevated intracranial pressure symptoms such as headache, nausea, and vomiting may coexist. Acute or recent-onset headaches (onset after age 50 years) that progress to intractable headaches, headaches that awaken patients from sleep, or headaches accompanied by focal, cognitive, or behavioral symptoms should trigger further evaluation for a brain tumor. Seizures occur in 20% to 40% of patients with glioblastomas, usually with a focal onset.[15]

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Brain MRI with contrast is the diagnostic modality of choice rather than CT scan, which provides limited information for the diagnosis and management of patients with glioblastomas and is reserved for patients with a contraindication for MRI. MRI typically shows an infiltrative, heterogeneous, ring-enhancing lesion with central areas of necrosis on T1-weighted imaging. Surrounding hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images represents white matter edema, infiltrating nonenhancing tumor, or a combination of both. Diffusion-weighted imaging may be helpful to differentiate glioblastomas from CNS lymphomas or cerebral abscesses, both of which may demonstrate restricted central diffusion.[16] Per the 2021 World Health Organization (WHO) classification,[17] a high-grade glioma that meets the molecular definition (*TERT* promoter variation, *EGFR* gene amplification, +7/-10 chromosome copy-number changes) but lacks the classical histologic microvascular proliferation and necrosis is often referred to as a molecular glioblastoma and may show only faint or patchy contrast enhancement or may lack central necrosis, as described in **CASE 2-1**. Glioblastomas are often unifocal, but there can be smaller satellite areas of enhancement. Occasionally, MRI can show a nonenhancing or minimally enhancing lesion in an adult patient with a new-onset seizure, and the lesion can rapidly evolve in weeks to a ring-enhancing, necrotic lesion.

Frequently, these tumors are located in the subcortical white matter and deeper gray matter of the cerebral hemispheres, although they can infiltrate the adjacent cortex and the corpus callosum into the contralateral hemisphere. Glioblastomas can also affect the brainstem, cerebellum, and spinal cord; however, when lesions are found in the midline or close to it, physicians should consider *H3 K27*-altered gliomas and other gliomas. A few non-neoplastic diseases may radiographically mimic glioblastomas, including brain abscesses, subacute stroke, and multiple sclerosis, resulting in a possible misdiagnosis. Considering the patient's age and history, as well as imaging features, before proceeding with surgery is critical. If the patient does not improve on the appropriate treatment or certain features of the history do not match, a short-term follow-up MRI is recommended. Additional workup including lumbar puncture, total spine MRI, or body positron emission tomography (PET) is, in general, not indicated.

Symptomatic Management

Corticosteroids may provide temporary symptomatic relief because they decrease peritumoral edema, but the ultimate goal is to proceed with specific antitumor therapies. The steroid dexamethasone is preferred because of its low mineralocorticoid activity, long half-life, and high bioavailability.[18] Typically, patients start taking dexamethasone at a total daily dose of 12 mg to 16 mg, but lower doses of 4 mg to 8 mg usually provide effective symptom management. Because of long-term side effects, including adrenal insufficiency (which may exacerbate fatigue and cognitive disturbance), diabetes, increased risk for infections, and bone fractures, the author recommends the minimum dexamethasone dose for the shortest possible period of time that provides symptom control. If a primary CNS lymphoma is suspected, dexamethasone should not be started until after the biopsy to avoid diagnostic delays because steroids may disrupt cellular morphology, potentially resulting in a nondiagnostic pathologic specimen.[19,20]

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Seizures and antiseizure medications are a significant source of morbidity in patients with brain tumors.[21,22] The 2021 Society for Neuro-Oncology and European Association of Neuro-Oncology practice guideline update recommends against prescribing antiseizure medications to reduce the risk of seizures in patients with newly diagnosed brain tumors who have never had a seizure.[23] Additionally, there is insufficient evidence to recommend prescribing antiseizure medications to reduce the risk of seizures in these patients in perioperative and postoperative settings or to support using tumor location, histology, grade, or molecular or imaging features when deciding whether or not to prescribe prophylactic antiseizure medications. When antiseizure medications are indicated, physicians may consider the use of nonhepatic microsomal enzyme-inducing antiseizure agents such as levetiracetam or lacosamide over older antiseizure medications to reduce side effects and drug interactions. For more information about seizures and antiseizure medications in patients with brain tumors, refer to the article "Management of Complications in Neuro-oncology Patients," by Mary R. Welch, MD, MS,[24] in this issue of *Continuum*.

Disease-modifying Treatment

Surgical resection followed by adjuvant radiotherapy combined with chemotherapy remains the backbone therapeutic strategy and should be considered in all patients with a newly diagnosed glioblastoma.

NEUROSURGICAL MANAGEMENT. The recommended neurosurgical approach for patients with a suspected glioblastoma is microsurgical resection aiming for maximal safe resection. A safe resection is important because postoperative morbidity can also contribute to a poor outcome.[25] Resection provides tissue for histologic and molecular diagnosis and may increase the patient's chances for clinical trial eligibility. Additionally, cytoreduction relieves mass effect, improving symptoms and allowing a rapid postoperative dexamethasone reduction or discontinuation. For unresectable tumors, stereotactic biopsy should be considered although the tissue volume is, in general, insufficient for molecular diagnosis. Laser interstitial thermal ablation may be a valuable initial treatment for patients who are ineligible for open resection.[26] Whenever possible, patients should receive surgery in facilities that provide advanced surgical tools (eg, 5-aminolevulinic acid, awake mapping, and functional and intraoperative MRI) and a dedicated support team (anesthesia and neuro-intensive care unit). The extent of resection is associated with overall survival in patients with glioblastomas.[27-29] It is also recommended to obtain a brain MRI with contrast within the first 48 to 72 hours after resection to evaluate any residual tumor. A recent report of the Response Assessment in Neuro-Oncology resect group suggests that the absolute residual tumor volume rather than the proportion of removed tumor might be prognostically more relevant and that this prognostic value is independent from molecular or clinical markers.[30]

RADIATION AND CHEMOTHERAPY FOR NEWLY DIAGNOSED GLIOBLASTOMAS. After resection or biopsy, the next treatment step includes adjuvant radiation therapy and concurrent oral chemotherapy with the DNA-alkylating agent temozolomide. The standard radiation therapy dose is 60 Gy divided in to 30 fractions (daily treatment, 5 days a week for 6 weeks). Radiation therapy

KEY POINTS

- MRI with contrast is the preferred imaging study when glioblastoma is suspected.
- MRI in patients with glioblastomas typically shows an infiltrative, heterogeneous, ring-enhancing lesion with central areas of necrosis on T1-weighted imaging with surrounding hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images.
- Molecular pathology is a key component of the integrated diagnosis of glioblastomas.
- The 2021 Society for Neuro-Oncology and European Association of Neuro-Oncology practice guideline update recommends against prescribing antiseizure medications to reduce the risk of seizures in patients with newly diagnosed brain tumors who have never had a seizure.
- Perioperative antiseizure medications are not recommended for patients with brain tumors who have never had a seizure.
- Surgical resection followed by adjuvant radiotherapy combined with chemotherapy should be considered in all patients with newly diagnosed glioblastoma.
- Maximal safe resection is the recommended neurosurgical approach for glioblastomas. The extent of resection is associated with overall survival.

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volumes (enhancing and nonenhancing), defined based on postoperative MRI, include the volume of abnormalities on T1-weighted MRI with contrast and T2-weighted MRI plus a margin of 1 cm to 3 cm. There is no role for stereotactic radiosurgery in newly diagnosed glioblastomas because gliomas are by definition infiltrating tumors.[31,32] Temozolomide is given on a continuous daily dose schedule, 7 days a week for the same 6 weeks at a dose of 75 mg/m^2/d.[33] This dosage is followed by six adjuvant temozolomide cycles (28-day cycle, 5 days on and 23 days off) at 150 mg/m^2/d for 5 days for cycle 1 and 200 mg/m^2/d for 5 days for cycles 2 through 6 (if tolerated). Common adverse effects of temozolomide are fatigue, nausea, constipation, and bone marrow toxicities, with lymphopenia and thrombocytopenia being the most common cytopenias. Temozolomide has been the recommended chemotherapy for newly diagnosed glioblastomas since 2005. A randomized clinical trial commonly known as the

CASE 2-1

A 64-year-old man presented with a new-onset seizure and cognitive impairment. Brain MRI demonstrated an infiltrative mass centered in the right frontoparietal white matter, with a small focus enhancement involving the right lateral frontoparietal juxtacortical white matter (FIGURE 2-1). The patient underwent biopsy of the tumor, which targeted the enhancing component. Pathology showed an *IDH*-wildtype astrocytic neoplasm with no mitosis, necrosis, or microvascular proliferation. Next-generation sequencing showed that the tumor was *IDH*-wildtype and contained a *TERT* promoter variation with no *MGMT* promoter methylation. By the 2021 World Health Organization (WHO) classification, the integrated diagnosis was glioblastoma, *IDH*-wildtype, *TERT* promoter mutant, CNS WHO grade 4.[3] The patient received treatment with radiation therapy (60 Gy in 30 fractions) with concurrent temozolomide, followed by six adjuvant temozolomide cycles with tumor-treating fields. However, the patient presented with disease progression 1 year later.

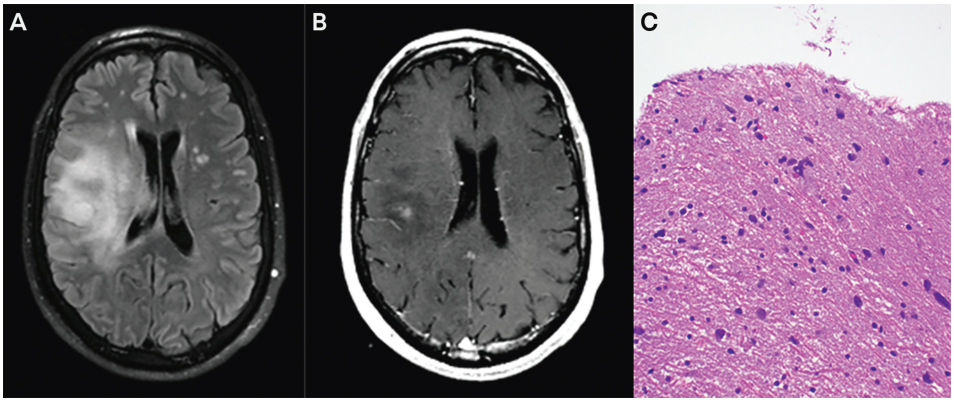

FIGURE 2-1
MRI and histology of the patient in CASE 2-1. Axial fluid-attenuated inversion recovery (FLAIR) (*A*) and axial postcontrast T1-weighted (*B*) brain MRI shows an infiltrating mass centered in the right frontoparietal region with an associated subcentimeter focus of enhancement. Hematoxylin and eosin (H&E) stain (*C*) along with other stains (*not shown*) demonstrate a histologically low-grade astrocytic neoplasm with no mitoses, tumor necrosis, or microvascular proliferation.

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Stupp protocol compared temozolomide administered concurrently and after radiation therapy with radiation therapy alone. Results showed an improvement in overall survival time (14.6 months versus 12.1 months) and absolute increases in 2- and 5-year survival. Patients with *MGMT* promoter methylation had an 8-month improvement in overall survival time versus a 1-month improvement in overall survival time for patients with an unmethylated *MGMT* promoter.[33,34] The marginal benefit of temozolomide for patients with an unmethylated *MGMT* promoter raises the question of whether it should be used in this patient population, particularly in clinical trials.

Black and Hispanic people have been reported to be less likely to receive radiation and chemotherapy compared with White non-Hispanic people. Time to treatment (radiation, chemotherapy, or both) initiation was longer in both groups compared with White non-Hispanic individuals.[35]

COMMENT

This case illustrates how the 2021 WHO classification of central nervous system (CNS) tumors provides more accurate prognostication and guidance for treatment options.[3] In the past, this case would have been classified as a low-grade astrocytoma by histology (*IDH*-wildtype astrocytic neoplasm with no mitosis, necrosis, or vascular proliferation) but, based on the molecular profile diagnosis, was updated to a CNS WHO grade 4 glioblastoma because the tumor cells were positive for *TERT* promoter variation. The higher grade was also reflected in the rapid progression at 1 year, typically uncommon for a lower-grade tumor. This case also shows that MRIs of patients with glioblastomas may show only faint or patchy contrast enhancement in contrast with the typical and well-known infiltrative, heterogeneous, ring-enhancing lesion with central areas of necrosis.

According to the 2021 WHO classification of CNS tumors, *IDH*-wildtype glioblastoma is a diffuse, astrocytic glioma that is *IDH*-wildtype and *H3*-wildtype and has one or more of the following histologic or genetic features: microvascular proliferation, necrosis, *TERT* promoter variation, *EGFR* gene amplification, or +7/-10 chromosome copy-number changes.[3] *MGMT* promoter methylation is an independent prognostic factor for longer overall survival in glioblastomas and a strong predictive marker for response to alkylating chemotherapy.

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TUMOR-TREATING FIELDS. Tumor-treating fields deliver low-intensity, intermediate-frequency (200 Hz), alternating electric fields that can disrupt cell division. Four transducer arrays are applied to the shaved scalp and worn for at least 18 hours a day. The US Food and Drug Administration (FDA) has approved tumor-treating fields for use in patients with newly diagnosed glioblastomas along with temozolomide after radiation therapy, based on the data from a randomized clinical trial that showed improvement in overall survival time (24.5 months for adjuvant temozolomide cycles plus tumor-treating fields versus 19.8 months for adjuvant temozolomide cycles alone) and the 2-year survival rate.[36] These modest results and patient concerns about quality of life have precluded a widespread adoption of this therapy. Ongoing studies may further clarify the role of this new treatment modality.[36,37]

OLDER ADULT PATIENTS WITH GLIOBLASTOMAS. Older adult patients with glioblastomas are generally defined as patients older than 60 years, 65 years, or 70 years, depending on the study.[38-41] Older age is one of the most significant negative prognostic factors for patients with glioblastomas.[39] Treating older adults with glioblastomas adds challenges to an already complex disease because of poor prognosis, frequent comorbidities, and increased risks of toxic effects from radiation therapy on the aging brain and chemotherapy on aging bone marrow. For patients 65 years old or older who are not candidates for standard 60-Gy radiation therapy, recommended treatment includes a hypofractionated (abbreviated) course of radiation therapy (40 Gy in 15 fractions over 3 weeks) with concurrent and adjuvant temozolomide. Single-modality treatment may be considered based on *MGMT* promoter methylation status for older patients who are not good candidates for combination therapy. For older patients with *MGMT* promoter unmethylated glioblastomas, hypofractionated radiation therapy alone (without temozolomide) is a treatment to consider. For older patients with *MGMT* promoter methylated glioblastomas, temozolomide alone is a reasonable option. Supportive care may be considered for older patients with glioblastomas with poor performance status or with severe concerns about toxicity or prognosis.[42]

TABLE 2-1 **Frequently Used Chemotherapy Regimens for Recurrent or Progressive Glioblastomas**

Drug	Drug class	Common or severe adverse effects	Common dosages and schedule
Lomustine (CCNU)	Alkylating agent	Bone marrow toxicity, fatigue	110 mg/m^2 on day 1 every 6-8 weeks
Bevacizumab	Antiangiogenic agent (monoclonal antibody)	Hypertension, proteinuria, thromboembolic events, wound healing delays	10 mg/kg every 2 weeks
Temozolomide	Alkylating agent	Cytopenias (mainly lymphopenia, less commonly thrombocytopenia), fatigue, nausea, vomiting	50 mg/m^2 on continuous daily schedule 75 mg/m^2 on days 1-21 every 4 weeks 150 mg/m^2 on days 1-7 every 2 weeks
Carmustine (BCNU)	Alkylating agent	Bone marrow toxicity, fatigue, pulmonary fibrosis	200 mg/m^2 on day 1 every 6-8 weeks

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RECURRENT OR PROGRESSIVE GLIOBLASTOMAS. Despite initial multimodality treatment, including surgery, radiation therapy, chemotherapy, and tumor-treating fields, glioblastomas eventually progress in virtually every patient. The median survival time for patients with recurrent glioblastomas who are enrolled in clinical trials is approximately 9 months.[43] Patients with poor prognostic factors have worse survival outcomes. Although clinical trials have assessed a variety of agents, including targeted therapy, immunotherapy, and viral therapy, no therapy has improved overall survival in this population. Patients with good performance status who are eligible and willing to participate in clinical trials should be encouraged to do so. Patients who are not eligible or interested in being part of these studies may consider the therapeutic options included in TABLE 2-1.

IDH-MUTANT GLIOMAS

Adult *IDH*-mutant gliomas are diffusely infiltrating primary brain tumors defined by the presence of somatic variations in the genes encoding isocitrate dehydrogenase 1 (IDH1) or isocitrate dehydrogenase 2 (IDH2) enzymes.

Overview and Epidemiology

The identification of *IDH* variations in gliomas represents one of the major hallmarks in the field of neuro-oncology in recent decades, leading to significant progress in terms of glioma classification and prognosis and potential novel therapeutic approaches. The IDH enzymes catalyze the oxidative decarboxylation of isocitrate to produce α-ketoglutarate, one of the rate-limiting steps of the tricarboxylic acid cycle, but when the enzymes are mutated, they have a neomorphic activity, which includes the conversion of α-ketoglutarate into the oncometabolite D-2-hydroxyglutarate (D2HG).[6,44] As a result, D2HG accumulates at supraphysiologic levels, and the concentration of α-ketoglutarate greatly decreases intracellularly. Several lines of evidence support the prominent role of *IDH* variations in the pathogenesis of these tumors and identify D2HG as the critical mediator in this complex process.[44-49]

Brain tumors with *IDH* variations are diffusely infiltrating gliomas, including *IDH*-mutant astrocytomas (CNS WHO grade 2-4) and *IDH*-mutant, 1p-19q co-deleted oligodendrogliomas (CNS WHO grade 2-3), which together account for approximately 4.6% of all primary brain tumors and 12% of all gliomas diagnosed in 2018.[50] Based on the Central Brain Tumor Registry of the United States dataset, the incidence of *IDH*-mutant gliomas was highest among patients 35 years to 44 years old with peaks between 30 years and 34 years for astrocytomas and between 40 years and 44 years for oligodendrogliomas. *IDH*-mutant gliomas have a higher incidence in males than in females and are more common in White individuals compared with individuals from other racial groups.[50] The same risk factors discussed for glioblastomas apply to *IDH*-mutant gliomas. In addition, Ollier disease, a skeletal disorder associated with somatic mosaic *IDH* variations, is linked to an increased risk of developing *IDH*-mutant gliomas.

Diagnosis

IDH-mutant gliomas typically have a more indolent biological behavior and are more epileptogenic than *IDH*-wildtype gliomas.[15] As many as 80% of astrocytomas and oligodendrogliomas may initially present with seizure, often

KEY POINTS

- Radiation therapy and temozolomide is the consensus best treatment for newly diagnosed glioblastomas after surgical resection or biopsy. The benefit of temozolomide is limited in patients with *MGMT* promoter unmethylated glioblastomas.
- Older patients with glioblastomas have a worse prognosis, and a hypofractionated course of radiation therapy with temozolomide, single-modality treatment, or supportive care may be considered.
- The identification of *IDH* variations in gliomas represents one of the major hallmarks in the field of neuro-oncology in recent decades, leading to significant progress in terms of glioma classification and prognosis and potential novel therapeutic approaches.
- Tumors with *IDH* variations accounted for 4.6% of all brain tumors and 12% of gliomas diagnosed in 2018.

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without other focal signs or symptoms.[51] Some patients (mainly with CNS WHO grade 3-4 *IDH*-mutant gliomas) may present with gradually progressive symptoms and more subtle focal deficits compared with patients with glioblastomas. As with glioblastomas, symptoms of *IDH*-mutant gliomas are often related to the tumor's anatomic location. In certain patients, physicians identify these tumors incidentally in brain images requested for reasons unrelated to the brain tumor (eg, motor vehicle accident, sports trauma).

Brain MRI with contrast is the diagnostic modality of choice for *IDH*-mutant gliomas, which are commonly located in the frontal lobes but can involve any region of the CNS, including the brainstem and spinal cord. MRI images typically show expansile lesions with a hyperintense signal in T2-weighted and FLAIR images involving both the cortex and underlying white matter. The presence of the T2-FLAIR mismatch sign (the presence of a complete or near-complete hyperintense signal on T2-weighted images and a relatively hypointense signal on FLAIR images, except for a hyperintense peripheral rim) has been described as highly specific for astrocytomas.[52] Oligodendrogliomas more frequently involve the cortex and may present with calcifications. Most grade 2 tumors are nonenhancing, but grade 3-4 astrocytomas and grade 3 oligodendrogliomas commonly enhance or have an enhancing component within a larger nonenhancing tumor. Advanced MRI techniques, including MR spectroscopy, have been investigated for noninvasive diagnosis and assessment of treatment response. Because the oncometabolite D2HG accumulates in *IDH*-mutant tumors and can be detected and measured noninvasively through D2HG MR spectroscopy, this technique represents a valuable tool in clinical practice.[53-56] Further developments are ongoing to increase the sensitivity of this method.

Glioma diagnosis does not rely solely on imaging. Both histologic and molecular data are essential for diagnosis, classification, and grading of

TABLE 2-2 **World Health Organization Grading Criteria for Astrocytoma, *IDH*-Mutant[a]**

Grade	Criteria
CNS WHO grade 2	A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* variation that is well differentiated and lacks histologic features of anaplasia
	Mitotic activity is not detected or very low
	Microvascular proliferation, necrosis, and homozygous deletions of *CDKN2A*, *CDKN2B*, or both are absent
CNS WHO grade 3	A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* variation that exhibits focal or dispersed anaplasia and displays significant mitotic activity
	Microvascular proliferation, necrosis, and homozygous deletions of *CDKN2A*, *CDKN2B*, or both are absent
CNS WHO grade 4	A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* variation that exhibits microvascular proliferation, necrosis, or homozygous deletion of *CDKN2A*, *CDKN2B*, or both, or any combination of these features

CNS = central nervous system; WHO = World Health Organization.
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IDH-mutant gliomas. In astrocytomas, *IDH1* or *IDH2* variations are accompanied by *ATRX* variations (resulting in nuclear loss of *ATRX* expression) and *TP53* variations (resulting frequently in strong nuclear p53 expression). Infratentorial *IDH*-mutant astrocytomas have a high frequency of noncanonical *IDH* variations and much lower incidence of *ATRX* variations. The diagnosis of oligodendroglioma requires an *IDH1* or *IDH2* variation along with 1p-19q co-deletion. In most cases, oligodendrogliomas also have *TERT* promoter hotspot variations and frequently *CIC* or *FUBP1* variations. TABLE 2-2 describes the grading criteria for *IDH*-mutant astrocytomas. Grading criteria for *IDH*-mutant, 1p-19q co-deleted oligodendrogliomas has not been well defined as these tumors comprise a continuous spectrum of tumors, ranging from well-differentiated, slow-growing tumors to frankly malignant tumors with rapid growth. Histologic features that have been linked to higher-grade tumors are high cellularity, marked cytological atypia, brisk mitotic activity, pathologic microvascular proliferation, and necrosis with or without palisading. The Symptomatic Management subsection of the Glioblastomas section also applies to *IDH*-mutant gliomas.

KEY POINTS

- Histologic and molecular features are essential to confirm the diagnosis in *IDH*-mutant gliomas.
- Because the oncometabolite D-2 hydroxyglutarate (D2HG) accumulates in *IDH*-mutant tumors and can be detected and measured noninvasively through D2HG MR spectroscopy, this technique represents a valuable tool in clinical practice.
- The extent of surgical resection has a significant effect on the clinical outcomes for both low-grade and high-grade gliomas, particularly in *IDH*-mutant astrocytomas.

Neurosurgical Management

Extensive surgical resection targeting all of the enhancing components, if present, and the nonenhancing disease (versus biopsy only) represents a critical first step in the management of *IDH*-mutant gliomas. Resection not only provides tissue for histologic and molecular diagnosis, but it also reduces seizure frequency and improves clinical outcomes.[57-59] The extent of surgical resection has a significant effect on the clinical outcomes for both low-grade and high-grade gliomas, particularly in *IDH*-mutant astrocytomas.[60-62] The extension of the resection needed outside the border of visible tumor (supramaximal resection) to achieve better outcomes is still unclear. A postoperative brain MRI with contrast should be obtained 24 to 48 hours after surgery to evaluate the extent of resection and residual disease. Differentiating residual nonenhancing tumor from postoperative cerebral edema is challenging, so a follow-up brain MRI with contrast obtained 1 to 2 months after resection may provide an even more accurate assessment of the residual tumor.

Postsurgical Management For Newly Diagnosed *IDH*-Mutant Glioma

Postsurgical management for newly diagnosed *IDH*-mutant glioma remains a controversial topic. The debate mainly focuses on radiation therapy timing, optimal dose of radiation therapy and target volume, and chemotherapy of choice.

RADIATION FOR *IDH*-MUTANT GLIOMAS. Postoperative radiation therapy and alkylating-based chemotherapy regimens are recommended for all *IDH*-mutant CNS WHO grade 3-4 gliomas and the majority of *IDH*-mutant CNS WHO grade 2 gliomas. Patients with what has been called low-risk *IDH*-mutant, CNS WHO grade 2 gliomas can be observed off treatment. Traditionally, low-risk patients have been those who had a gross total resection with good performance status, were positive for 1p-19q co-deletion, and were younger than 40 years old. However, it is important to emphasize that in this context there is no consensus regarding the definition of low-risk and these recommendations are based on

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trials designed before the molecular era and the updated WHO classification of CNS tumors.[3] Furthermore, debate exists as to whether grade 2 and grade 3 CNS WHO grade 2-3 *IDH*-mutant gliomas truly behave differently. The reason to delay radiation therapy in selected patients with CNS WHO grade 2 gliomas is to preserve cognitive function.

Experts continue to discuss the optimal dose of radiation therapy and target volume. For CNS WHO grade 2 *IDH*-mutant gliomas, a dose of 45 Gy to 54 Gy in 1.8 Gy in daily fractions is recommended. For CNS WHO grade 3-4 *IDH*-mutant gliomas, 59.4 Gy to 60 Gy in 1.8 Gy to 2.0 Gy daily fractions is recommended.[63] Short-term radiation–induced toxicities include fatigue, headache, skin erythema, otitis, and alopecia. Long-term radiation–induced toxicities include radiation necrosis (0% to 13% with higher doses, and oligodendroglioma histology is associated with increased risk), cognitive decline, decreased health-related quality of life, and less commonly strokelike migraine attacks after radiation therapy.[64-66] When available, proton therapy (rather than commonly used photon radiation therapy) may be considered for certain patients with *IDH*-mutant gliomas. Proton therapy allows for high doses to target the tumor with lower doses directed to normal tissue and vulnerable areas, such as the optic chiasm, optic nerves, and hippocampus. Another important phenomenon after radiation therapy is pseudoprogression, which refers to MRI findings that mimic disease progression with or without clinical deterioration and occurs a few weeks to months after radiation therapy completion.[67]

CHEMOTHERAPY FOR *IDH*-MUTANT GLIOMAS. Radiation therapy followed by alkylating-based chemotherapy should be offered to all non–low-risk patients. For oligodendrogliomas (CNS WHO grade 2 to 3), a combination of procarbazine, lomustine (CCNU), and vincristine is the recommended chemotherapeutic approach.[42,68-70] The expected toxicity from this regimen includes fatigue, weight loss, nausea, and cytopenias.[68] Two potential toxicities are particularly relevant for the neurologist, often resulting in a consultation in the inpatient or outpatient setting. First, procarbazine may possess some monoamine oxidase inhibitor (MAOI) activity. Following an MAOI diet (ie, avoiding tyramine-containing foods) and carefully reviewing drug interactions is recommended to avoid hypertension and serotonin syndrome. Second, vincristine-induced peripheral neuropathy occurs in virtually all patients who receive this drug. Initially, patients report paresthesia in their fingertips and feet, with or without pain. The severity of the symptoms is dose related, but symptoms may occur even after the first dose. Neurophysiologic studies are compatible with a symmetric, primarily axonal neuropathy. In general, the drug should be discontinued once the patient reports neuropathic symptoms. Vincristine-induced peripheral neuropathy is usually reversible, but improvement is gradual and may take many months. Currently, there is no effective prophylaxis for vincristine-induced peripheral neuropathy.[71] Adjuvant temozolomide is a reasonable alternative to procarbazine, lomustine (CCNU), and vincristine when toxicity is a concern.[42] The ongoing Radiation Therapy With Concomitant and Adjuvant Temozolomide Versus Radiation Therapy With Adjuvant PCV Chemotherapy in Patients With Anaplastic Glioma or Low Grade Glioma (CODEL) trial is assessing radiation therapy plus procarbazine

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lomustine (CCNU), and vincristine versus radiation therapy plus temozolomide in CNS WHO grade 2-3 oligodendrogliomas and will clarify the role of these two chemotherapy regimens.[72]

Therapy for *IDH*-mutant astrocytomas (CNS WHO grade 2) includes radiation therapy with adjuvant chemotherapy (temozolomide or procarbazine, lomustine [CCNU], and vincristine).[42,68,73] Physicians should discuss the potential risks and benefits of both options with the patient, including the level of evidence supporting each option.

Based on the Phase III Trial of Anaplastic Glioma Without 1p/19q Loss of Heterozygosity (LOH) (CATNON) trial, treatment recommendations for *IDH*-mutant CNS WHO grade 3 astrocytomas include radiation therapy with adjuvant temozolomide.[74] *IDH*-mutant CNS WHO grade 4 astrocytomas may be treated like an *IDH*-mutant CNS WHO grade 3 astrocytoma with radiation therapy followed by temozolomide or, like an *IDH*-wildtype glioblastoma, with radiation therapy and concurrent temozolomide followed by adjuvant temozolomide.[33,74]

INHIBITORS OF MUTANT ISOCITRATE DEHYDROGENASE. The role of IDH inhibitors in *IDH*-mutant gliomas has been under investigation for over a decade.[75-79] Vorasidenib, an oral brain-penetrant inhibitor of IDH1 and IDH2 enzymes, was assessed in a double-blind, randomized, placebo-controlled, phase 3 study in patients with residual or recurrent *IDH*-mutant CNS WHO grade 2 gliomas who had undergone surgery as their only previous treatment, but who had not received radiation therapy or chemotherapy.[80] Progression-free survival was significantly longer in the vorasidenib arm (median progression-free survival time: 27.7 months) than in the placebo arm (median progression-free survival time: 11.1 months). Vorasidenib was well tolerated. Results for the overall survival endpoints remain to be determined.

TREATMENT AT PROGRESSION. Although a variety of therapeutic strategies are available at the time of progression, including resection, chemotherapy, and radiation therapy. Depending on the initial treatment that the patient received, none of these options have a curative intention. Patients should consider participating in clinical trials whenever possible, as many of the ongoing trials were designed based on *IDH*-mutant glioma vulnerabilities and may include treatment with immunotherapies, targeted therapies, vaccine therapies, or a combination of these therapies. Re-resection, rechallenge with alkylating agents (temozolomide or lomustine [CCNU]), and repeat radiation therapy may be considered in patients who are not eligible or not interested in clinical trials.

BRAF-ALTERED GLIOMAS

B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) represents a novel target in gliomas. $BRAF^{V600}$ variations occur in approximately 3% of glioblastomas and much more frequently in circumscribed gliomas, including pleomorphic xanthoastrocytomas (60% to 80%), gangliogliomas (20% to 70%), and pilocytic astrocytomas (10%).[81-83] *BRAF* variations are mutually exclusive with *IDH* variations in gliomas, and their prognostic significance is still unclear and may vary with histologic subtype. Studies confirm the clinical and radiographic benefit in *BRAF*-mutated low-grade and high-grade gliomas,

KEY POINTS

- **Short-term radiation–induced toxicities include fatigue, headache, skin erythema, otitis, and alopecia.**
- **Long-term radiation–induced toxicities include radiation necrosis, cognitive decline, decreased health-related quality of life, and less commonly strokelike migraine attacks after radiation therapy.**
- **Vincristine-induced peripheral neuropathy is usually reversible, but improvement is gradual and may take many months.**

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including glioblastomas when treated with BRAF and MEK inhibitors.[84-86] Based on these results, the FDA recently approved the combination of dabrafenib and trametinib for the treatment of advanced solid tumors including gliomas with *BRAF* variations.[87] CASE 2-2 illustrates the use of dabrafenib and trametinib in a patient with a *BRAF*-mutant glioblastoma.

GLIOMAS WITH NTRK FUSION

Neurotrophic tyrosine receptor kinase (NTRK) fusions have been identified with a low frequency in a variety of adult primary brain tumors, including

CASE 2-2

A 25-year-old woman presented with a new-onset seizure. Her brain MRI showed a right temporal enhancing lesion. She underwent gross total resection. The pathology was read as *IDH*-wildtype glioblastoma, central nervous system World Health Organization grade 4, and sequencing showed that tumor cells were positive for a *BRAF*^{V600E} variation. She received treatment with radiation therapy (60 Gy in 30 fractions) with concurrent temozolomide followed by six adjuvant temozolomide cycles. Despite initial treatment, 2 years later she presented with clinical deterioration and MRI showed distant left parietal tumor recurrence (FIGURE 2-2A and 2-2B). She was treated with dabrafenib and trametinib, achieving a prolonged partial response (FIGURE 2-2C and 2-2D). Two years after treatment initiation, she continued on dabrafenib and trametinib, remained radiographically stable, and was clinically asymptomatic.

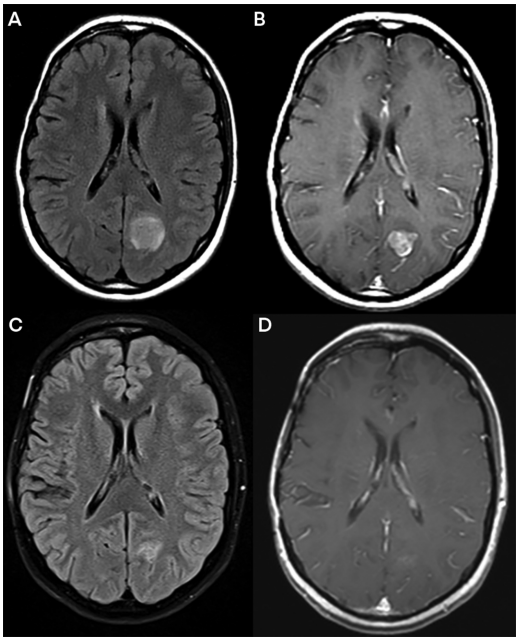

FIGURE 2-2
Imaging of the patient in CASE 2-2. Baseline axial fluid-attenuated inversion recovery (FLAIR) (*A*) and postcontrast T1-weighted (*B*) MRI before starting dabrafenib and trametinib show a new enhancing lesion in the left parietal lobe. Axial FLAIR (*C*) and postcontrast T1-weighted (*D*) MRI done 2 years later show prolonged partial response with near-complete resolution of the enhancing component.

COMMENT

This case illustrates the importance of molecular characterization in these incurable tumors to be able to identify rare but targetable alterations such as *BRAF* variations.

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IDH-wildtype glioblastomas, low-grade gliomas, pilocytic astrocytomas, and gangliogliomas, as well as in pediatric CNS tumors.[88-91] NTRK inhibitors, such as larotrectinib and entrectinib, have received regulatory approval based on high efficacy in tumors harboring NTRK fusions, regardless of the tumor site, including CNS tumors, highlighting the importance of tumor profiling.[92,93] Larotrectinib was the first tissue-agnostic molecularly targeted therapy approved by the FDA for the treatment of cancer. Clinical trials with next-generation NTRK inhibitors are ongoing to address tumor resistance to first-generation drugs.

FUTURE DIRECTIONS

Gliomas represent a widely heterogeneous group of tumors. Scientists expect more diffuse glioma subgroups will emerge in the next decade within the current three groups established by the 2021 WHO classification of CNS tumors.[3] The recommended treatment, including surgery, radiation therapy, chemotherapy, and tumor-treating fields (in glioblastomas), provides limited benefits to patients with gliomas. As a result, a variety of clinical trials are ongoing to identify more effective therapies for selected patient subgroups. Current trials include targeted therapies, immunotherapies, viral therapies, and a combination of the above. It is also important to emphasize that the neuro-oncology field is evolving in terms of clinical trial design to develop more informative trials, including window-of-opportunity arms that can confirm the biological effect of the therapy and its ability to penetrate the brain, as well as platform trials that can improve clinical trial process efficiency and have more inclusive and flexible eligibility criteria, allowing more patients to participate.

CONCLUSION

The neuro-oncology field has advanced significantly over the past decades in understanding tumor biology and molecular pathology and translating these findings into more accurate prognostication and tumor classification. However, very limited improvement has been made in terms of additional survival benefit for these patients, and gliomas remain an incurable group of tumors. Ongoing research efforts have incorporated this recent knowledge along with innovative clinical trial designs, such as window-of-opportunity arms and adaptive randomization, to develop and test new therapies for specific glioma subtypes.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Pediatric Neuro-oncology

By Fatema Malbari, MD

ABSTRACT

OBJECTIVE: **This article reviews the most common pediatric brain tumors, neurocutaneous syndromes, treatment-related neurotoxicities, and the long-term outcomes of survivors.**

LATEST DEVELOPMENTS: **In the era of molecular diagnostics, the classification, management, and prognostication of pediatric brain tumors and neurocutaneous syndromes has been refined, resulting in advancements in patient management. Molecular diagnostics have been incorporated into the most recent World Health Organization 2021 classification. This knowledge has allowed for novel therapeutic approaches targeting the biology of these tumors with the intent to improve overall survival, decrease treatment-related morbidity, and improve quality of life. Advances in management have led to better survival, but mortality remains high and significant morbidity persists. Current clinical trials focus on tumor biology targeted therapy, deescalation of therapy, and multimodal intensified approaches with targeted therapy in more high-risk tumors.**

ESSENTIAL POINTS: **Molecular diagnostics for pediatric brain tumors and neurocutaneous syndromes have led to novel therapeutic approaches targeting the biology of these tumors with the goals of improving overall survival and decreasing treatment-related morbidity. Further understanding will lead to continued refinement and improvement of tumor classification, management, and prognostication.**

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Dr Malbari reports no disclosure.

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INTRODUCTION

Central nervous system (CNS) tumors are the most common solid tumors in children and young adults (0 to 19 years old) and are the leading cause of childhood (0 to 14 years old) cancer-related mortality.[1] The annual incidence of CNS tumors in children and young adults is 6.23 per 100,000 people. Gliomas are the most frequent tumor histology reported and high-grade gliomas are the leading cause of cancer mortality in children. Tumor histology and location vary depending on age (FIGURE 3-1 and TABLE 3-1). Gliomas are most commonly seen in children from ages 0 to 14 years. Embryonal tumors are the second most frequent in the 0-to-9-year-old age group, with atypical teratoid/rhabdoid tumors most common in infants younger than 1 year old and medulloblastoma in the 1-to-4-year-old age group. Pituitary tumors are more common than gliomas in adolescents and young adults (14 to 19 years old). The most frequent tumor location for children and young adults is the pituitary gland and craniopharyngeal duct, followed by the cerebellum. Brainstem tumors account

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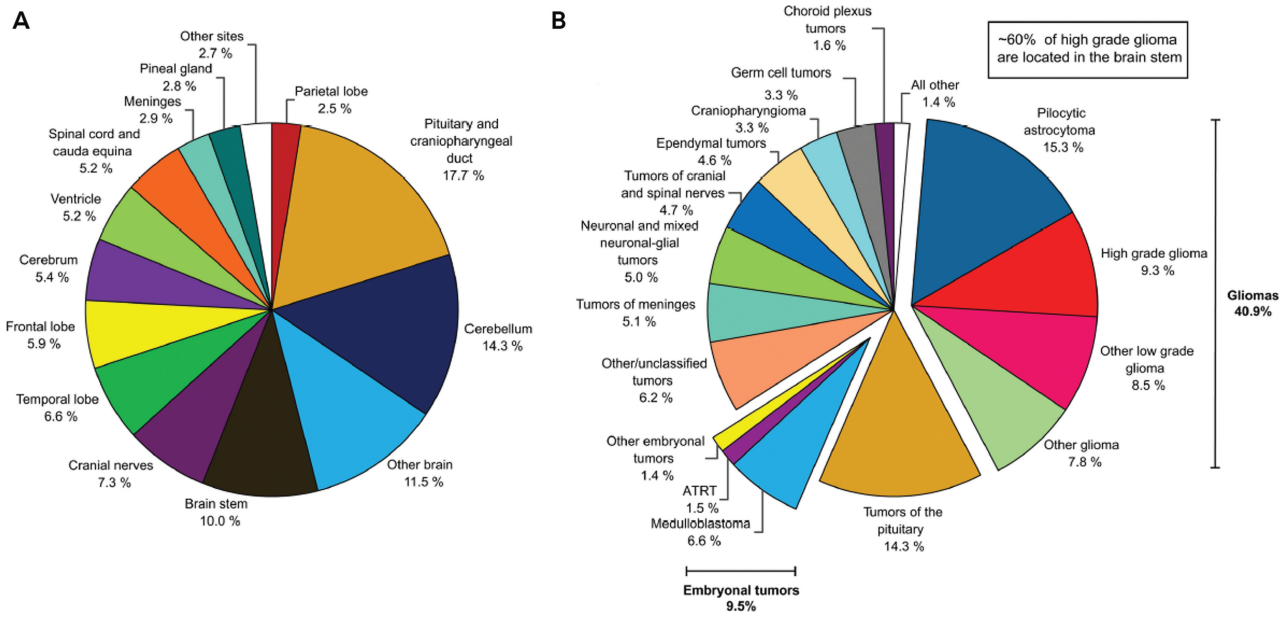
A
Other sites 2.7 %
Pineal gland 2.8 %
Meninges 2.9 %
Spinal cord and cauda equina 5.2 %
Ventricle 5.2 %
Cerebrum 5.4 %
Frontal lobe 5.9 %
Temporal lobe 6.6 %
Cranial nerves 7.3 %
Brain stem 10.0 %
Other brain 11.5 %
Cerebellum 14.3 %
Pituitary and craniopharyngeal duct 17.7 %
Parietal lobe 2.5 %
B
~60% of high grade glioma are located in the brain stem
Choroid plexus tumors 1.6 %
Germ cell tumors 3.3 %
Craniopharyngioma 3.3 %
Ependymal tumors 4.6 %
Tumors of cranial and spinal nerves 4.7 %
Neuronal and mixed neuronal-glial tumors 5.0 %
Tumors of meninges 5.1 %
Other/unclassified tumors 6.2 %
Other embryonal tumors 1.4 %
ATRT 1.5 %
Medulloblastoma 6.6 %
Embryonal tumors 9.5%
All other 1.4 %
Pilocytic astrocytoma 15.3 %
High grade glioma 9.3 %
Other low grade glioma 8.5 %
Other glioma 7.8 %
Gliomas 40.9%
Tumors of the pituitary 14.3 %

FIGURE 3-1

Distribution in children and adolescents ages 0 to 19 years of all primary malignant and nonmalignant brain and other central nervous system tumors by site (*A*) and histopathology (*B*) (5-year total = 25,497; annual average cases = 5099).

ATRT = atypical teratoid/rhabdoid tumor.

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for 60% of all high-grade gliomas and are associated with the highest rate of mortality in children and young adults.

Risk factors for the development of pediatric CNS tumors remain largely unknown, aside from prior ionizing-radiation exposure. Several genetic syndromes such as neurofibromatosis, tuberous sclerosis complex, Li-Fraumeni syndrome, constitutional mismatch repair deficiency, Gorlin syndrome, and Turcot syndrome increase the risk for the development of brain tumors.[1,2] The diagnostic imaging modality of choice is MRI; however, in emergent clinical situations a CT scan should be obtained first. In addition to an MRI of the brain, imaging of the entire neuraxis at diagnosis is often recommended due to the higher risk of leptomeningeal dissemination in children.[3] Management of pediatric CNS tumors utilizes a multimodal approach. Treatments can include surgery, radiation therapy (RT), chemotherapy, and targeted therapy either singly or in various combinations depending on tumor histopathology and stage and the age of the patient. Although overall survival for patients with certain pediatric CNS tumors has improved, mortality remains high for patients with other tumors, and treatment-related and tumor-related morbidities persist. Common long-term effects include neurocognitive impairment, neuroendocrine dysfunction, and focal neurologic deficits. With recent advances in the molecular characterization of tumors, targeted therapy is being evaluated and may potentially mitigate treatment-associated morbidity. This article reviews the most common pediatric CNS tumors, neurocutaneous and cancer predisposition syndromes, and the long-term effects of these tumors and their therapies.

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GLIOMAS

Pediatric gliomas are the most common pediatric CNS tumors, representing approximately 40% of all CNS tumors.[1] Histologically, they are comprised of astrocytic or mixed glial-neuronal cells. Gliomas can be subdivided into low grade and high grade. Pediatric gliomas are clinically, biologically, and molecularly distinct from adult gliomas.

Low-Grade Gliomas

Low-grade gliomas comprise approximately 30% of all CNS tumors.[4] Glial tumors include pilocytic astrocytomas, which are the most common low-grade glioma (36%), pleomorphic xanthoastrocytomas, diffuse astrocytomas, oligodendrogliomas, and subependymal giant cell astrocytomas (SEGAs), which occur almost exclusively in patients with tuberous sclerosis. Mixed glial-neuronal tumors include gangliogliomas, dysembryoplastic neuroepithelial tumors, angiocentric gliomas, glioneuronal tumors, polymorphous low-grade neuroepithelial tumors of the young, and desmoplastic infantile gangliogliomas. Pediatric low-grade glioma molecular alterations involve the RAS–mitogen-activated protein kinase (MAPK) pathway, most commonly involving *BRAF* (KIAA1549 fusion or V600E variation) or *NF1* germline variations.[4] There are other less common alterations (eg, MYB, MYBL1, IDH1, H3F3A), including many

TABLE 3-1 **Pediatric Central Nervous System Tumor Type and Location**

Location	Tumor type
Supratentorial	
Suprasellar	Germ cell tumor, craniopharyngioma, pituitary tumor, meningioma
Optic nerve	Glioma (pilocytic astrocytoma)
Cortex	Glioma (CNS WHO grade 1-4), embryonal tumor (except medulloblastoma), ependymoma, ganglioglioma, dysembryoplastic neuroepithelial tumor, desmoplastic infantile ganglioglioma, glioneuronal tumor
Ventricles	Choroid plexus tumor, ependymoma, meningioma
Pineal region	Germ cell tumor, embryonal tumor (including pineoblastoma), glioma (tectal)
Thalamus or midline	Giloma (pilocytic astrocytoma, diffuse midline)
Infratentorial	
Cerebellum	Glioma (CNS WHO grade 1-4), embryonal tumor (including medulloblastoma), ependymoma, meningioma
Brainstem	Glioma (exophytic pilocytic astrocytoma, diffuse midline)
Spinal cord	Glioma (CNS WHO grade 1-4), ependymoma, meningioma, embryonal tumor

CNS = central nervous system; WHO = World Health Organization.

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that involve the RAS-MAPK pathway (eg, FGFR, NTRK, RAF, ALK, ROS, PI3K).[4] *IDH* variations occur in 70% to 80% of adult low-grade gliomas but less than 1% of pediatric low-grade gliomas. In tuberous sclerosis complex, SEGAs develop secondary to a disruption in the mammalian target of the rapamycin (mTOR) pathway.

The clinical presentation of pediatric low-grade gliomas is dependent on tumor location, which can be anywhere in the CNS. Cerebral hemisphere tumors typically manifest with focal neurologic deficits, such as seizures and headache. Posterior fossa tumors present with cerebellar signs and increased intracranial pressure. Diencephalic tumors can present with failure to thrive. Although pediatric low-grade gliomas are often well circumscribed and localized, about 2% to 5% of patients at initial diagnosis and 5% to 12% at the time of progression will have disseminated disease.[5]

Pilocytic astrocytomas (CNS World Health Organization [WHO] grade 1) most frequently arise in the cerebellum and diencephalon and often occur between ages 5 and 14 years.[6] On MRI, pilocytic astrocytomas will appear as a cystic lesion with a mural-enhancing nodule. This imaging finding is also typical for pleomorphic xanthoastrocytomas, hemangioblastomas, and gangliogliomas. Histologically, pilocytic astrocytomas have a biphasic architecture with Rosenthal fibers and eosinophilic granular bodies. The most common molecular alteration in pilocytic astrocytomas is *BRAF-KIAA1549* fusion (approximately 80%).[4]

Diffuse low-grade gliomas (CNS WHO grade 2) represent 6% of all pediatric low-grade gliomas, arising frequently in the cerebral hemispheres. On MRI, these tumors are poorly defined, lobulated, and infiltrative. Their mitotic index is low and molecularly they have an *MYB* or *MYBL1* alteration. Pleomorphic xanthoastrocytomas (CNS WHO grades 2 and 3) are pediatric low-grade gliomas (accounting for approximately 1% of all pediatric CNS tumors) that arise in the cerebral hemispheres, frequently the temporal lobe, and can present with seizures, with a peak incidence between the second and third decades of life.[7] Histologically, these are pleomorphic cellular tumors with xanthomatous (lipid-laden) astrocytes. The presence of necrosis and high mitotic activity are characteristic of a CNS WHO grade 3 pleomorphic xanthoastrocytoma. $BRAF^{V600E}$ variations (10%) are seen in 60% of pleomorphic xanthoastrocytomas.[4] Of the mixed glial neuronal tumors, gangliogliomas are the most common, representing 11% of pediatric low-grade gliomas. Gangliogliomas occur in children and young adults; arise from the cerebral hemispheres, often the temporal lobe; and patients can present with seizures. On histology, ganglion cells in addition to neoplastic glial cells (astrocytes, oligodendrocytes) can be seen.[8] $BRAF^{V600E}$ variations are found in approximately 40% to 50% of these tumors as well. Desmoplastic infantile gangliogliomas (CNS WHO grade 1), a rare pediatric low-grade glioma (less than 1% of this group), present in infants as a large hemispheric lesion, often with seizures. Angiocentric gliomas, also a rare hemispheric pediatric low-grade glioma (less than 1% of these tumors), present with refractory epilepsy.

Dysembryoplastic neuroepithelial tumors (CNS WHO grade 1) represent about 4% of all pediatric low-grade gliomas, with a peak incidence from 10 to 14 years and a predilection for the temporal lobe.[4,8] Patients will often present with seizures that can be refractory, and surgical resection can help with seizure control. These tumors are frequently associated with cortical dysplasia and

KEY POINTS

- Central nervous system (CNS) tumors are the most common solid tumors in children and young adults (ages 0 to 19 years) and are the leading cause of childhood (ages 0 to 14 years) cancer-related mortality.
- Although overall survival for patients with certain pediatric CNS tumors has improved, mortality remains high for patients with other tumors, and treatment-related and tumor-related morbidity persists.
- Pediatric gliomas are the most common pediatric CNS tumor, representing approximately 40% of all CNS tumors.
- Pediatric low-grade glioma molecular alterations involve the RAS-mitogen activated protein kinase pathway, most commonly involving *BRAF* (KIAA1549 fusion or V600E variation) or *NF1* germline variations.
- Management of pediatric low-grade gliomas is dependent on tumor location and characteristics and patient age.
- Neurocutaneous conditions, such as neurofibromatosis type 1 and tuberous sclerosis complex, are associated with an increased risk of developing pediatric low-grade gliomas.

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radiologically are well-circumscribed, cystic, T2-weighted hyperintense, bubbly appearing lesions. Histologically, dysembryoplastic neuroepithelial tumors have oligodendroglial-like cells and floating neurons with or without cortical dysplasia and are characterized by *FGFR* variations. Oligodendrogliomas represent 3% of all pediatric low-grade gliomas. These tumors arise in the cerebral hemispheres and patients also present with seizures.

Management of pediatric low-grade gliomas is dependent on tumor location and characteristics and the age of the patient. Gross total resection can be curative with a low risk of recurrence, a 5-year progression-free survival of 94%, and a 10-year overall survival of 84% to 96%.[9] For unresectable tumors, close surveillance is indicated. However, treatment options for progressive tumors include chemotherapy, radiation therapy, and targeted therapy.[9] Patients with residual or progressive disease can have chronic difficulties and subsequently a worsened quality of life from the associated morbidity of the tumor and treatment.

RT for these patients can achieve similar results to gross total resection, with a 5-year progression-free survival and overall survival of 87% and 96%, respectively.[9] However, RT can cause significant adverse effects such as neurocognitive impairment, vasculopathies, secondary malignancies, and endocrine and growth deficiencies. For this reason, radiation is often reserved for children older than 10 years to limit long-term neurocognitive deficits, for patients who have already exhausted other treatment options, or in cases where RT may cause minimal toxicity. Chemotherapy is the recommended option when gross total resection is not feasible, although this may change with the availability of targeted therapies.

There are a few different first-line chemotherapy options for patients with these tumors, and although none are as effective as surgery or radiation they can achieve about 50% to 80% progression-free survival at 3 years.[9] The most common chemotherapy regimens are carboplatin and vincristine or vinblastine. As pediatric low-grade gliomas almost universally involve variations in the RAS-MAPK pathway, MAPK/extracellular signal-regulated kinase inhibitors and BRAF inhibitors have shown promising results.[9] Current phase 3 clinical trials randomize conventional chemotherapy and targeted therapies in patients with newly diagnosed or previously untreated pediatric low-grade gliomas with BRAF alterations due to encouraging results from prior clinical trials in patients with recurrent or refractory pediatric low-grade gliomas.

Neurocutaneous conditions, such as neurofibromatosis type 1 (NF1) and tuberous sclerosis complex, are associated with an increased risk of developing pediatric low-grade gliomas. A pilocytic astrocytoma of the optic pathway can develop in 15% to 20% of patients with NF1 (**CASE 3-1**).[10,11] About 30% to 50% of these patients will be symptomatic, with the greatest risk being for those under 6 years old, and 33% will need treatment.[10] Chemotherapy is the first-line option as surgery is generally not feasible and RT can cause an increased risk of secondary malignancies and vasculopathy, especially in patients with NF1. Targeted therapy with MAPK/extracellular signal-regulated kinase inhibitors has shown clinical and radiographic responses in patients with plexiform neurofibromas and optic pathway gliomas in NF1 and is now being investigated as first-line therapy in a phase 3 trial for NF1-associated optic pathway gliomas. NF1 is the most common neurocutaneous syndrome with an estimated prevalence of 1 in 3000. It is an autosomal dominant tumor predisposition

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syndrome, although 40% to 50% of patients can have a sporadic gene variation. In addition to optic pathway gliomas, patients are at an increased risk of developing low-grade gliomas in other locations such as the brainstem, high-grade gliomas, plexiform neurofibromas, and malignant peripheral nerve sheath tumors. Other neurologic symptoms include neurodevelopmental and cognitive disabilities (20% of affected patients with learning disorders, 75% requiring school accommodations), cerebrovascular disorders (2% to 5%), and epilepsy (4% to 13%).[11,12]

Tuberous sclerosis complex is the second most common neurocutaneous syndrome with an estimated incidence of 1 in 6000 to 10,000. Although tuberous sclerosis complex is inherited in an autosomal dominant manner, two-thirds of affected individuals have a sporadic or de novo variation.[13] CNS manifestations of tuberous sclerosis complex include cortical tubers (90%), subependymal nodules (80%), epilepsy (approximately 75% to 90%, often refractory), autism (21%), attention deficit hyperactivity disorder (19%), anxiety (33%), impulsivity (43%), sleep difficulties (44%), and academic difficulties (59%) (TABLE 3-2[14]).[15,16]

SEGAs (CNS WHO grade 1) can occur in 10% to 15% of patients with tuberous sclerosis complex and are most prevalent before age 25 years, and 10% are symptomatic.[15] Surgical resection is indicated for symptomatic patients with acute focal neurologic deficits or obstructive hydrocephalus. If a patient has an asymptomatic growing or large SEGA, mild to moderate symptoms, or is not a surgical candidate, targeted therapy with mTOR inhibitors is recommended.[13]

High-Grade Gliomas

Pediatric high-grade gliomas (CNS WHO grades 3 and 4) represent about 10% of pediatric CNS tumors and are the leading cause of cancer-related mortality in children under 19 years old, despite advances in management.[1] The 2-year overall survival in patients with hemispheric tumors is 32% and in patients with midline tumors excluding the brainstem it is 21%. Sixty percent of all pediatric high-grade gliomas are located in the brainstem, which is associated with a 2-year overall survival of 5% (diffuse intrinsic pontine gliomas) (CASE 3-2). Children younger than 1 year old have an overall better prognosis in all tumor locations, with a 2-year overall survival of 61%.[19] Four different pediatric diffuse high-grade glioma groups have been defined in the WHO 2021 classification: (1) diffuse midline glioma H3 K27-altered, (2) diffuse hemispheric glioma H3 G34-mutant, (3) diffuse pediatric-type high-grade glioma H3-wildtype (WT) and *IDH*-WT, and (4) infant-type hemispheric glioma.[20] Recurrent histone variations in H3.3 and H3.1 have been identified in pediatric high-grade gliomas. Diffuse midline gliomas located in the pons, thalamus, or spinal cord are commonly associated with a K27M variation in histone 3. Hemispheric gliomas frequently have a G34R variation in histone 3.[19,21] High-grade gliomas that are both WT for histone 3 and IDH are driven by $BRAF^{V600E}$, *NF1*, and receptor like tyrosine kinase (*RYK*) variations. Unlike adult high-grade gliomas, *IDH* variations are found in fewer than 5% of pediatric high-grade gliomas, but the presence of this variation does portend a 1-year overall survival of 100%.[22] *MGMT* promoter methylation is less common than in adult high-grade gliomas and occurs in H3G34R-mutant and *IDH1*-mutant tumors. Infant-type hemispheric gliomas are associated with variations in *RYK*.[19]

The clinical presentation is dependent on tumor location and can include signs of increased intracranial pressure or focal neurologic deficits, typically of short

KEY POINTS

- The revised diagnostic criteria for neurofibromatosis type 1 include confirmation of a heterozygous *NF1* deletion, a parent with neurofibromatosis type 1, and two or more choroidal anomalies.
- Pediatric high-grade gliomas (CNS World Health Organization grades 3 and 4) represent about 10% of pediatric CNS tumors and are the leading cause of cancer-related mortality in children younger than 19 years old, despite advances in management.
- Four different pediatric diffuse high-grade glioma groups have been defined in the World Health Organization 2021 classification: 1) diffuse midline glioma H3 K27-altered, 2) diffuse hemispheric glioma H3 G34-mutant, 3) diffuse pediatric-type high-grade glioma H3-wildtype and isocitrate dehydrogenase wildtype, and 4) infant-type hemispheric glioma.

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CASE 3-1

An 18-month-old boy was referred for evaluation of developmental delay. On examination, he had ten café au lait macules (>5 mm in diameter) and macrocephaly. Given the concern for possible neurofibromatosis type 1 (NF1), he was referred to an ophthalmologist who noted two choroidal abnormalities, described as bright, patchy nodules, seen on optical coherence tomography. Based on these findings, he met the revised diagnostic criteria for NF1 (FIGURE 3-2). One year later, his parents noted a bulging of his left eye and examination revealed inflammation of the left optic nerve. An MRI of the brain confirmed bilateral optic nerve lesions, greater on the left than the right, extending to the chiasm (FIGURE 3-3). He was followed with ophthalmic examinations and MRIs and was subsequently started on chemotherapy due to concerns for progressive vision impairment. He completed chemotherapy without any adverse events and had continued stability of his vision and optic pathway gliomas.

COMMENT

This is a typical example of a patient with NF1 and an optic pathway glioma and highlights the revised diagnostic criteria established in 2021. The revision allows for earlier diagnosis and better differentiation from other conditions with similar skin stigmata (FIGURE 3-2).[17] Many NF1 features are age dependent, with café au lait macules presenting within the first year of life. About 80% of patients with multiple café au lait macules at 1 year old are ultimately diagnosed with NF1. Plexiform neurofibromas are generally congenital but only occur in 50% of patients and are externally visible in 25% to 30%.[18] In the absence of a parent (revised from a first-degree relative) with the diagnosis of NF1, most children do not meet the criteria until 6 years old when other common manifestations are present. For this reason, genetic testing with confirmation of a heterozygous NF1 deletion was added to allow for an earlier diagnosis. In addition, the presence of two or more choroidal anomalies was added since this anomaly was found to be more common than Lisch nodules and can be detected as young as 2 years old, instead of 4 to 5 years old.[18] It is rare to see choroidal anomalies in patients who do not have NF1, and they typically present as a single lesion. It is important to distinguish NF1 from Legius syndrome and constitutional mismatch repair deficiency. Patients with Legius syndrome have café au lait macules and learning disabilities with or without axillary or inguinal freckling, while patients with constitutional mismatch repair deficiency only have café au lait macules.

The revised diagnostic criteria for NF1 include confirmation of a heterozygous *NF1* deletion, a parent with NF1 or *NF2*-related schwannomatosis, or two or more choroidal anomalies.

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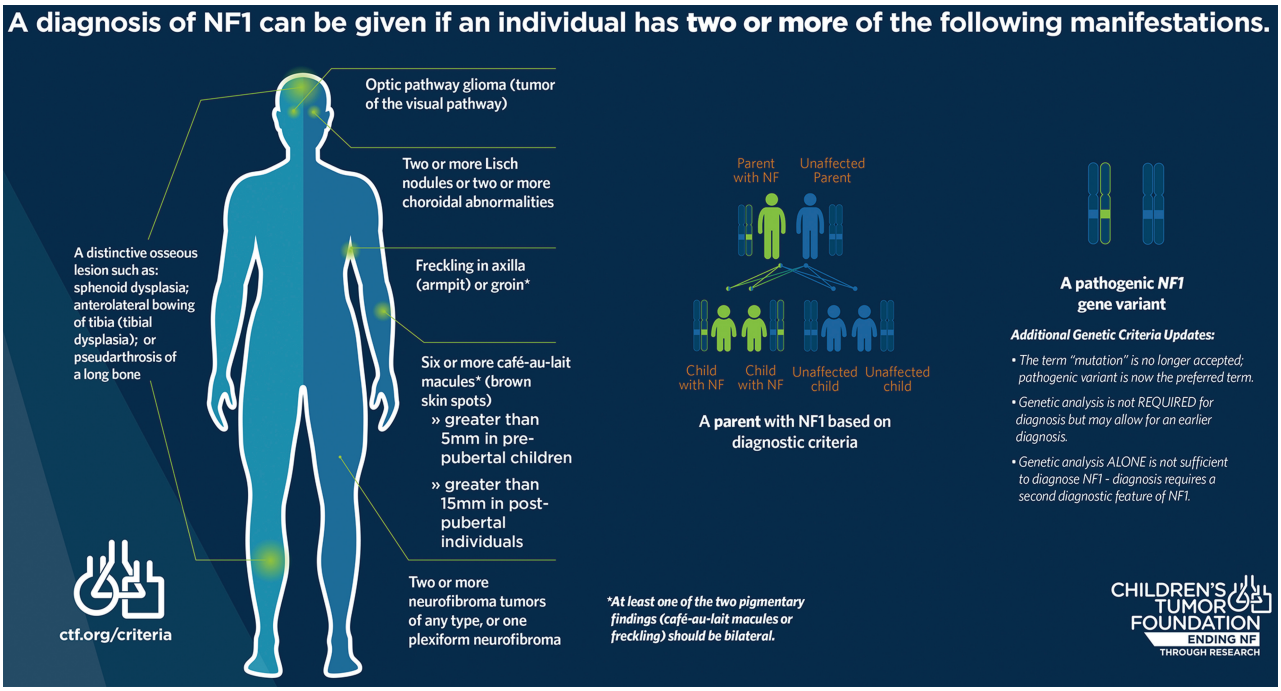
A diagnosis of NF1 can be given if an individual has two or more of the following manifestations.
Optic pathway glioma (tumor of the visual pathway)
Two or more Lisch nodules or two or more choroidal abnormalities
Freckling in axilla (armpit) or groin*
Six or more café-au-lait macules* (brown skin spots)
» greater than 5mm in pre-pubertal children
» greater than 15mm in post-pubertal individuals
Two or more neurofibroma tumors of any type, or one plexiform neurofibroma
A distinctive osseous lesion such as: sphenoid dysplasia; anterolateral bowing of tibia (tibial dysplasia); or pseudarthrosis of a long bone
ctf.org/criteria
Parent with NF
Unaffected Parent
Child with NF
Child with NF
Unaffected child
Unaffected child
A parent with NF1 based on diagnostic criteria
A pathogenic NF1 gene variant
Additional Genetic Criteria Updates:
• The term "mutation" is no longer accepted; pathogenic variant is now the preferred term.
• Genetic analysis is not REQUIRED for diagnosis but may allow for an earlier diagnosis.
• Genetic analysis ALONE is not sufficient to diagnose NF1 - diagnosis requires a second diagnostic feature of NF1.
*At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.
CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

FIGURE 3-2

Clinical and genetic diagnostic criteria for neurofibromatosis type 1.

Infographic courtesy of the Children's Tumor Foundation.[101]

NF1 = neurofibromatosis type 1.

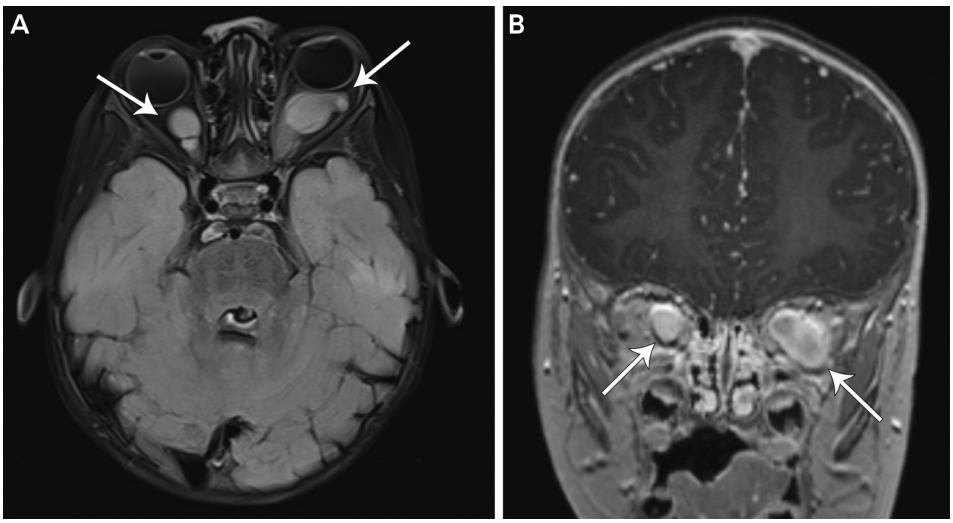

FIGURE 3-3

Neurofibromatosis type 1–associated optic pathway glioma. Axial fluid-attenuated inversion recovery (FLAIR) (*A*) and coronal postcontrast T1-weighted MRI (*B*) show bilateral optic nerve lesions (*A*, *B*, *arrows*), larger on the left than on the right, extending to the chiasm, with contrast enhancement.

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duration. Patients with brainstem pediatric high-grade gliomas present with rapid-onset cranial nerve deficits, long tract signs, ataxia, and obstructive hydrocephalus. H3 K27-altered diffuse midline gliomas most frequently present in younger children; the median age for brainstem tumors is 5 years, while that of all other diffuse midline gliomas is 7.4 years. These tumors are associated with a poor prognosis, with a median overall survival time of brainstem pediatric high-grade gliomas of 10.8 months and all other midline pediatric high-grade gliomas of 13.5 months.[19] Diagnostic criteria for diffuse midline gliomas include a midline glioma that is diffuse and has an H3K27M variation. Biopsies are being offered more routinely since confirmation of an H3K27M variation is required for enrollment in some clinical trials. Hemispheric pediatric high-grade gliomas occur in adolescents and young adults, often in the temporal and parietal lobes, and patients can present with hemiparesis, hemisensory loss, seizures, and

TABLE 3-2 **Clinical and Genetic Diagnostic Criteria of Tuberous Sclerosis Complex[a]**

Major features

- **Hypomelanotic macules (≥3; at least 5 mm diameter)**
- **Angiofibroma (≥3) or fibrous cephalic plaque**
- **Ungual fibromas (≥2)**
- **Shagreen patch**
- **Multiple retinal hamartomas**
- **Multiple cortical tubers or radial migration lines**
- **Subependymal nodule (≥2)**
- **Subependymal giant-cell astrocytoma**
- **Cardiac rhabdomyoma**
- **Lymphangioleiomyomatosis (LAM)[b]**
- **Angiomyolipomas (>2)[b]**

Minor features

- **"Confetti" skin lesions**
- **Dental enamel pits (>3)**
- **Intraoral fibromas (≥2)**
- **Retinal achromatic patch**
- **Multiple renal cysts**
- **Nonrenal hamartomas**
- **Sclerotic bone lesions**

Definite tuberous sclerosis complex: Two major features or one major feature with two minor features.
Possible tuberous sclerosis complex: Either one major feature or two or more minor features.
Genetic diagnosis: A pathogenic variant in *TSC1* or *TSC2* is diagnostic for tuberous sclerosis complex. Most tuberous sclerosis complex–causing variants are sequence variants that clearly prevent TSC1 or TSC2 protein production. Some variants compatible with protein production (eg, some missense changes) are well established as disease causing. Other variant types should be considered with caution.
[a] Reprinted from TSC Alliance.[14] © 2021 TSC Alliance.
[b] A combination of the two major clinical features LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis.

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increased intracranial pressure. The median overall survival time for patients with hemispheric pediatric high-grade gliomas is 18 months. Diffuse pediatric-type high-grade H3/*IDH*-WT gliomas are more heterogeneous, occurring in children, adolescents, and young adults, most often in the supratentorial region. The median overall survival time is 1.5 years; however, three different subgroups have been identified, each with different prognoses. Infant-type hemispheric gliomas are rare, typically occur within the first year of life, and are associated with the best prognosis. Patients may present with enlarging head circumference, failure to thrive, irritability, and increased intracranial pressure. Histologically, pediatric high-grade gliomas have pleomorphism, mitotic activity, and microvascular proliferation with or without necrosis.

The management of pediatric high-grade gliomas is maximal safe surgical resection followed by focal RT in children 3 years old or older. The extent of resection seems to affect overall survival and progression-free survival, with near to gross total resection associated with improved outcomes.[23] Focal RT is avoided or delayed in children younger than 3 years old due to concerns for RT-associated toxicity such as cognitive impairment, secondary tumors, vasculopathy, and neuroendocrine dysfunction. Optimal therapy for children younger than 3 years old is less clear. Multiple chemotherapy regimens have been tried in patients with these tumors without any significant improvement in overall survival and no standard chemotherapy approach has been identified. Treatment in young children consists of maximal safe surgical resection followed by observation alone, due to better prognosis in this age group, or standard-dose chemotherapy. The molecular classification of pediatric high-grade gliomas has identified potential targetable therapeutic options which are currently being explored. Some of these include targeting H3K27M-mutant tumors and *RYK* variations. In addition, immunotherapy and different delivery approaches of novel agents to bypass the blood-brain barrier are being investigated (eg, intra-arterial, convection-enhanced delivery, intranasal, intracavitary).[24]

Genetic cancer predisposition syndromes associated with the development of pediatric high-grade gliomas include Li-Fraumeni syndrome, constitutional mismatch repair deficiency, and Lynch syndrome. Li-Fraumeni syndrome is an autosomal dominant cancer predisposition syndrome associated with germline variations in *TP53*. Patients with Li-Fraumeni syndrome are predisposed to a variety of childhood malignancies including pediatric high-grade gliomas, choroid plexus carcinomas, and sonic hedgehog signaling molecule (*SHH*) medulloblastomas.[25] Li-Fraumeni syndrome is the underlying condition in 40% of patients with choroid plexus carcinomas and 10% of patients with *SHH* medulloblastomas. Choroid plexus tumors are rare, representing 1.6% of all CNS tumors in children 0 to 19 years old. They most commonly occur in children 3 years old or younger with the majority (approximately 10%) in children younger than 1 year old.[1] These tumors arise from the choroid plexus and patients will present with accelerated head growth or macrocephaly and signs of obstructive hydrocephalus with lethargy and vomiting. Choroid plexus tumors can be further classified as papillomas (CNS WHO grade 1), atypical papillomas (grade 2), and carcinomas (grade 3). On MRI, these tumors are intraventricular lobulated tumors with a cauliflowerlike appearance. Treatment for all Li-Fraumeni syndrome–associated tumors is generally maximal safe surgical resection with or without chemotherapy or radiation, depending on the age of

KEY POINTS

- **Management of pediatric high-grade gliomas includes maximal safe surgical resection followed by focal radiation therapy in children 3 years old or older.**
- **Genetic cancer predisposition syndromes associated with the development of pediatric high-grade gliomas include Li-Fraumeni syndrome, constitutional mismatch repair deficiency, and Lynch syndrome.**
- **Diffuse midline glioma of the pons remains an incurable diagnosis, with a median overall survival time of 11 months. Radiation therapy remains the standard treatment and can prolong life by an additional 3 to 4 months.**

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the child. Brain tumor surveillance in Li-Fraumeni syndrome includes yearly brain MRIs, initially with contrast and subsequently without if prior MRIs are normal.[25]

Constitutional mismatch repair deficiency is one of the most aggressive hereditary cancer predisposition syndromes and presents most often in childhood. It is associated with biallelic pathogenic variants in mismatch repair genes, most commonly in *PMS2*.[26] Constitutional mismatch repair deficiency has some overlapping features with NF1 including café au lait macules; however, in these patients they are more irregular with jagged borders and variable pigmentation and there are often fewer than six macules. In addition, these

CASE 3-2

A 5-year-old girl presented with a 2-week history of progressively worsening gait, blurry vision, drooling, and slurred speech. On examination, she had dysarthria, incomplete abduction of the right eye, mild flattening of the right nasolabial fold, and an unsteady gait. Neuroimaging revealed a large expansile mass involving the pons diffusely, encasing the basilar artery and demonstrating mass effect on the fourth ventricle (FIGURE 3-4). A radiographic diagnosis of diffuse midline glioma of the pons was made. A biopsy was completed to confirm the diagnosis and identify molecular alterations as the family was interested in pursuing clinical trials. Pathology confirmed a high-grade glioma (central nervous system World Health Organization grade 4) with an H3K27M variation. The child received focal radiation therapy (RT) and dexamethasone for symptom amelioration. She was weaned off dexamethasone after completing RT. She had some improvement overall and was enrolled in a clinical trial where she received therapy for 9 months before developing worsening symptoms concerning for tumor progression. She was started back on dexamethasone and received reirradiation, but unfortunately died 2 months later.

COMMENT

This case represents a characteristic presentation of diffuse midline glioma of the pons. Biopsies are being offered to identify molecular alterations as they are safe and feasible.[30] These results can potentially allow for additional clinical trial options for patients. Biopsies are elective and families who do not pursue them are still able to consider clinical trials that are not targeting molecular alterations. Diffuse midline glioma of the pons remains an incurable diagnosis, with a median overall survival time of 11 months.[31] RT remains the standard treatment and can prolong life by an additional 3 to 4 months. Reirradiation can be considered for patients who received initial radiation at least 6 months prior. Reirradiation is tolerable and can provide some symptomatic relief as well as minimal prolongation of survival time.[31,32] Steroids are widely prescribed as supportive or palliative treatment in these patients. However, prolonged steroid use can cause significant side effects and negatively impact quality of life and therefore should be used with caution.[33]

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patients can have neurofibromas and axillary freckling. CNS WHO grade 3 and 4 gliomas commonly occur in patients with constitutional mismatch repair deficiency who are younger than 25 years old. Surveillance for brain tumors includes brain MRI every 6 months starting at 2 years old.[27]

Lynch syndrome is an autosomal dominant cancer predisposition syndrome associated with a mismatch repair gene variation, most commonly monoallelic *MSH2* and *MLH1*. Unlike constitutional mismatch repair deficiency, brain tumors are infrequent in Lynch syndrome; rather, colorectal cancer is most closely associated with this syndrome. Gliomas are the most common type of brain tumor in these patients.[28] Surveillance screening for brain tumors is not

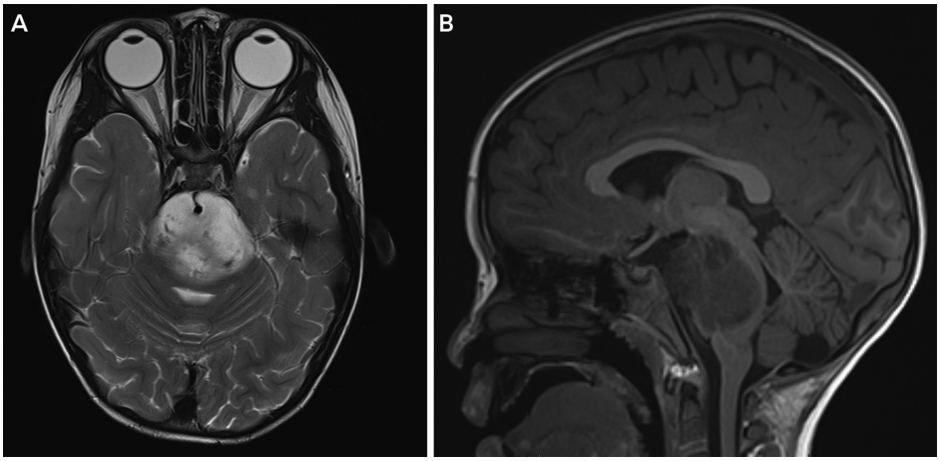

FIGURE 3-4
Imaging of the patient in CASE 3-2 showing diffuse midline glioma of the pons. Axial T2-weighted (*A*) and sagittal T1-weighted MRI (*B*) show a large expansile mass encasing the basilar artery with mass effect on the fourth ventricle involving the pons diffusely.

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indicated in Lynch syndrome and treatment is similar to that for sporadic pediatric high-grade gliomas, but they are often more resistant to therapy.[28] Clinical responses to immune checkpoint inhibition have been observed.[24,29] If there is a strong family history of Lynch syndrome–related cancers, one should consider further testing and screening for Lynch syndrome.

EMBRYONAL TUMORS

Embryonal tumors represent about 9.5% of all CNS tumors in patients 0 to 19 years old, most commonly in children 9 years old and younger.[1] Medulloblastomas are the most frequent CNS embryonal tumors in children 1 to 4 years old, representing 58% of all embryonal tumors in this age group.[1] Peak incidence is between 1 to 4 years old and 5 to 9 years old, with 6 years as the median age for diagnosis.[34] Medulloblastomas can rarely occur in adults. The most common embryonal tumors in children less than 1 year old are atypical teratoid/rhabdoid tumors.[1] Other rare embryonal tumors that can occur in children include embryonal tumors with multilayered rosettes.

Medulloblastomas generally arise from the cerebellum, can invade the fourth ventricle, and can present with CNS metastases in one-third of patients at the time of diagnosis. Therefore, complete tumor staging with an MRI of the spine and lumbar puncture for CSF cytology is necessary. Clinically, patients will present with symptoms concerning for increased intracranial pressure such as headaches, vomiting, altered mental status, and cerebellar dysfunction. Symptoms typically present over a few weeks to months. On MRI, medulloblastomas are heterogeneous tumors composed of cysts, calcifications, and necrosis. They can project into the fourth ventricle but not the basal cisterns, which is a more typical feature seen in ependymoma. On diffusion-weighted imaging (DWI), medulloblastomas have restricted diffusion due to the hypercellularity of these tumors which helps differentiate them from other posterior fossa tumors such as ependymomas and pilocytic astrocytomas (FIGURE 3-5).[35] Histologically, medulloblastomas are described as cellular small round blue cell tumors. Medulloblastomas can be further classified into four

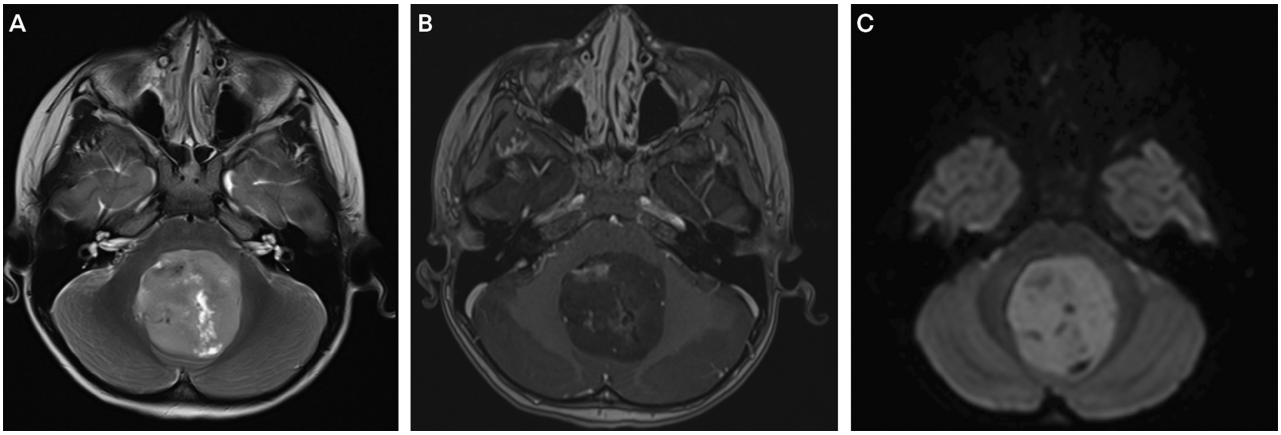

FIGURE 3-5

Imaging of a patient with a medulloblastoma. Axial T2-weighted (*A*) and axial postcontrast T1-weighted MRI (*B*) show a large 5-cm heterogeneously enhancing midline posterior fossa mass centered within the fourth ventricle, and diffusion-weighted imaging (*C*) shows restricted diffusion throughout.

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groups based on histopathology: classic, desmoplastic or nodular, medulloblastomas are with extensive nodularity, and large cell or anaplastic (combined). Molecularly, there are four distinct subgroups with different prognoses and this is how medulloblastomas are classified in the WHO classification: wingless (WNT), *SHH*, group 3, and group 4.[20,34]

The management of medulloblastomas consists of maximal safe surgical resection followed by risk-adapted craniospinal irradiation and adjuvant chemotherapy. Risk stratification is based on age, extent of surgical resection, presence of metastatic disease, histology, and molecular features. The overall survival at 5 years for medulloblastomas is greater than 90% in patients with low risk, 75% to 90% in patients with average risk, 50% to 75% in patients with high risk, and less than 50% in patients with very high risk.[36] Patients with average-risk medulloblastomas will receive lower doses of craniospinal irradiation in comparison to patients with high risk. Children younger than 3 years old will receive radiation-sparing therapy, such as high-dose chemotherapy regimens with or without autologous stem cell rescue, methotrexate, or focal radiation.[34]

The WNT molecular subgroup is associated with the best prognosis and is categorized as low risk, with a 5-year overall survival of 95%. It represents 10% of all medulloblastomas and these tumors are typically seen in older children and young adults. They are centrally located near the brainstem, are nonmetastatic, and most frequently have classic histology. Molecular alterations specific to WNT include monosomy 6 and a variation in *CTNNB1*.[34] Patients with *APC* germline variations or familial adenomatous polyposis (FAP) are at risk for the development of WNT medulloblastomas in adolescence and are treated the same as sporadic cases.[34] Deescalation of therapy consisting of lower doses of both craniospinal irradiation and chemotherapy is being investigated in the WNT medulloblastoma subgroup in an attempt to decrease toxicity and late effects while maintaining an excellent prognosis.[34]

The *SHH* molecular subgroup represents 30% of all medulloblastomas and occurs more frequently in children younger than 3 years old or older than 16 years old. These tumors usually arise from the cerebellar hemispheres and are often desmoplastic or medulloblastoma with extensive nodularity. *SHH* medulloblastomas can be further categorized into four different subtypes: SHH α, SHH β, SHH γ, and SHH δ.[37] Each subtype has a different age predilection and prognosis as well as various molecular changes. Treatment is being modified within this subgroup based on age, prognosis, and molecular changes. Adolescents and adults with *SHH* medulloblastomas will receive surgery, craniospinal irradiation, and chemotherapy with the addition of an *SHH* inhibitor in the setting of a clinical trial. *SHH* medulloblastomas can develop in infants with Gorlin syndrome which is caused by a *PTCH* or *SUFU* variation.[34] Treatment for patients with Gorlin syndrome also avoids radiation as they are at a greater risk for developing secondary basal cell carcinomas in the radiation field.

About 25% of patients with medulloblastomas are molecularly defined as group 3 and are typically young infants and children. These tumors are often midline, and in 40% of these patients metastatic disease is present at diagnosis with a 5-year overall survival of less than 60%.[34] Histology frequently demonstrates large cell anaplastic or classic characteristics. Different subtypes of group 3 are being proposed based on molecular alterations and outcomes. *MYC*

KEY POINTS

- **Molecularly, there are four distinct medulloblastoma subgroups with different prognoses in the World Health Organization classification: wingless, sonic hedgehog, group 3, and group 4.**
- **The treatment of medulloblastomas is associated with considerable toxicity and can reduce quality of life. Cerebellar mutism syndrome after surgical resection has been reported in approximately 34% of patients.**
- **Cerebellar mutism syndrome is a poorly understood constellation of symptoms including emotional lability, paucity of speech, apraxia, and cerebellar and cranial nerve dysfunction, and is associated with neurocognitive impairment.**
- **Atypical teratoid/rhabdoid tumors are highly aggressive embryonal tumors that most commonly affect young children (11% and 4% of children with brain tumors younger than 1 year old and between 1 to 4 years old, respectively), with a 5-year overall survival rate of 30% to 40%.**

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amplification and isochromosome 17q are molecular alterations seen in this subgroup. Treatment for high-risk patients includes surgery, high-dose craniospinal irradiation, and chemotherapy with the addition of novel targeted agents through clinical trials, or high-dose chemotherapy for infants.[34]

Group 4 is the most common subgroup, representing 35% of all medulloblastomas. These tumors typically occur in late childhood and early adolescence, arise from the midline, and are metastatic in one-third of patients. Group 4 medulloblastomas are associated with an intermediate prognosis which is dependent on the presence of metastatic disease and molecular alterations. Histology is often classic and this subgroup can be divided into additional subtypes based on molecular alterations. The low-risk group has chromosome 11 loss and the high-risk group has metastatic disease at diagnosis.[36] Treatment is dependent on risk stratification but includes surgery, risk-adapted craniospinal irradiation, and chemotherapy with the potential addition of novel agents for high-risk patients, offered through clinical trials.

The treatment of medulloblastomas is associated with considerable toxicity and can impair quality of life. Patients can develop cerebellar mutism syndrome after surgical resection, reported in approximately 34% of cases.[38] Cerebellar mutism syndrome is a constellation of symptoms that includes emotional lability and paucity of speech in addition to cerebellar and cranial nerve dysfunction. Patients with cerebellar mutism syndrome will have some recovery with supportive care; however, most have long-term significant neurocognitive impairment.[38] Cerebellar mutism syndrome remains a challenging condition with a limited understanding of its etiology, risk factors, and management. The underlying mechanism is not completely understood; however, the disruption of the cerebellar outflow tracts, the cerebellar nuclei, and their efferent projections through the superior cerebellar peduncle has been shown to correlate with the development of cerebellar mutism syndrome.[39,40] Symptoms occur 0 to 7 days after surgery, with the most definitive being speech and language difficulties, emotional lability, and apraxia.[38,41] Speech impairment is always transient with a median recovery time of 2 months.[38] There are no standardized treatment approaches for cerebellar mutism syndrome, although multidisciplinary supportive care is best. Patients will often need prolonged admission to an inpatient rehabilitation unit and medications to help manage symptoms like agitation, mood lability, behavior dysregulation, and inattention. Patients will have persistent neurologic symptoms and long-term neurocognitive deficits. Quality of life can be negatively impacted and the ability to carry out activities of daily living can be challenging, causing significant impact on patients and their families. Craniospinal irradiation can also cause neurocognitive impairment in addition to secondary malignancies, vasculopathy, and endocrine deficiencies. Chemotherapy regimens for medulloblastomas include vincristine and cisplatin which can cause neuropathy and ototoxicity. Medulloblastoma survivors often have a poorer quality of life.

Atypical teratoid/rhabdoid tumors are highly aggressive embryonal tumors that most commonly affect young children (11% and 4% of children with brain tumors younger than 1 year old and between 1 to 4 years old, respectively), with a 5-year overall survival rate of 30% to 40%.[42] They most frequently arise in the posterior fossa, followed by the supratentorial region and rarely the spinal cord. Metastatic disease can be present in 20% to 40% of patients at the time of

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diagnosis and therefore patients need to have a spine MRI and a lumbar puncture for staging. The clinical presentation for infratentorial tumors includes lethargy, vomiting, and cranial nerve deficits, and for supratentorial tumors headaches and focal weakness. On imaging, these tumors can look similar to medulloblastomas and be heterogeneous with cysts, calcifications, and hemorrhage. They will also have restricted diffusion on DWI. Histologically, these are also small round blue cell tumors with rhabdoid cells and require a loss of INI1 nuclear staining for diagnosis. Somatic gene variations associated with atypical teratoid/rhabdoid tumor include biallelic inactivation of *SMARCB1* on chromosome 22 and less frequently a *SMARCA4* variation.[43] One-third of patients will also have these germline variations. Further subgroupings of atypical teratoid/rhabdoid tumors based on molecular analyses and outcomes are being identified. The treatment of atypical teratoid/rhabdoid tumors has been challenging due to the young age of patients and the aggressive nature of the tumors. Multimodal therapy consisting of surgery, chemotherapy, high-dose chemotherapy, and focal radiation has shown improvement in overall survival.[42] RT has typically been avoided in younger children; however, some studies suggest no significant neurocognitive impairment with focal RT.[44] Targeted therapies are also being investigated through clinical trials.

KEY POINT

- Recurrence rates in ependymomas are high and can be delayed, up to 15 years after initial therapy.

EPENDYMOMAS

Ependymomas represent 5% of all pediatric CNS tumors with a peak incidence in early childhood. In children, these tumors frequently arise in the posterior fossa (60%) followed by the supratentorial region (30%), and less commonly in the spinal cord (10%), whereas in adults the most frequent location is the spinal cord.[45] Patients can have metastatic disease at the time of diagnosis and therefore staging with a spine MRI and lumbar puncture is necessary.

Clinical symptoms are dependent on tumor location, with infratentorial tumors often presenting with signs of increased intracranial pressure, cranial nerve palsies, and ataxia and supratentorial tumors presenting with focal neurologic deficits, headaches, and seizures. On imaging, ependymomas are heterogeneous tumors with areas of necrosis, calcification, cysts, and hemorrhage. Unlike medulloblastomas, in the posterior fossa these tumors can extend into the foramina of Luschka and Magendie. Restricted diffusion on DWI is seen only in anaplastic ependymomas, which can also help differentiate lower-grade ependymomas from medulloblastomas. Characteristic histologic features include ependymal rosettes and perivascular pseudorosettes.

In the most recent WHO classification, ependymomas are defined based on location and specific molecular characteristics. There are nine subgroups for ependymoma: (1) spinal, (2) posterior fossa, (3) supratentorial subependymoma (CNS WHO grade 1), which most commonly occurs in adults, (4) spinal myxopapillary ependymoma (now CNS WHO grade 2), (5) spinal ependymoma (CNS WHO grades 2 and 3), (6) posterior fossa ependymoma group A, (7) posterior fossa ependymoma group B, (8) supratentorial ependymoma *YAP1* fusion positive, and (9) *ZFTA-RELA* fusion positive. The *RELA* subgroup represents the majority of supratentorial ependymomas and occurs in all ages, while the supratentorial-*YAP1* subgroup is found mostly in pediatric patients.[46] Posterior fossa ependymoma group A tumors primarily occur in infants and young children, while posterior fossa ependymoma group B ependymomas are predominant in adolescents and young adults.[46] Supratentorial-ependymoma-*YAP1*

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CASE 3-3

A 14-year-old boy presented with a 10-day history of headaches, emesis, and fatigue. On examination, he was noted to have one hyperpigmented macule on the right lower extremity, concerns for decreased hearing, and brisk reflexes. A brain MRI showed a large left lateral intraventricular mass, bilateral acoustic nerve masses, a left middle cranial fossa mass, and a left cerebellar cystic mass (FIGURE 3-6). MRI of the spine revealed an intramedullary mass at the C2 to C3 level and numerous intradural extramedullary masses at the cervical, lumbar, and sacral levels (FIGURE 3-7). There was no family history of *NF2*-related schwannomatosis (NF2). Based on imaging, he met one of the criteria for the diagnosis of NF2: bilateral vestibular schwannomas. In addition, his MRI was suggestive of a large left intraventricular meningioma, left middle cranial fossa meningioma, left cerebellar meningioangiomatosis, intramedullary ependymoma, and intradural extramedullary schwannomas. Gross total resection of the ventricular mass was achieved and pathology confirmed a meningioma. He was followed in a multidisciplinary clinic with surveillance brain and spine imaging and audiology evaluations every 6 months.

COMMENT

This case highlights a typical patient with NF2 who has multiple central nervous system pathologies including a rare lesion, meningioangiomatosis, which has only been described in 200 cases.[50] Recently, revised diagnostic criteria and nomenclature for NF2 have been proposed (TABLE 3-3).[48] These criteria were derived by a modified Delphi process. The international group consensus recommendation was to propose renaming NF2 to *NF2*-related schwannomatosis due to overlapping features and the desire for a definition based on the genetic alteration. In addition, the diagnostic criteria were revised to minimize the requirements for diagnosis. To meet diagnostic criteria for *NF2*-related schwannomatosis, a patient would need (1) bilateral vestibular schwannomas (as in this case), (2) two anatomically distinct *NF2*-related tumors with identical *NF2* pathogenic variants, or (3) at least two major or one major and two minor criteria (TABLE 3-3). For patients with symptomatic tumors, surveillance is dependent on the clinical and radiographic findings, as in this case.[51]

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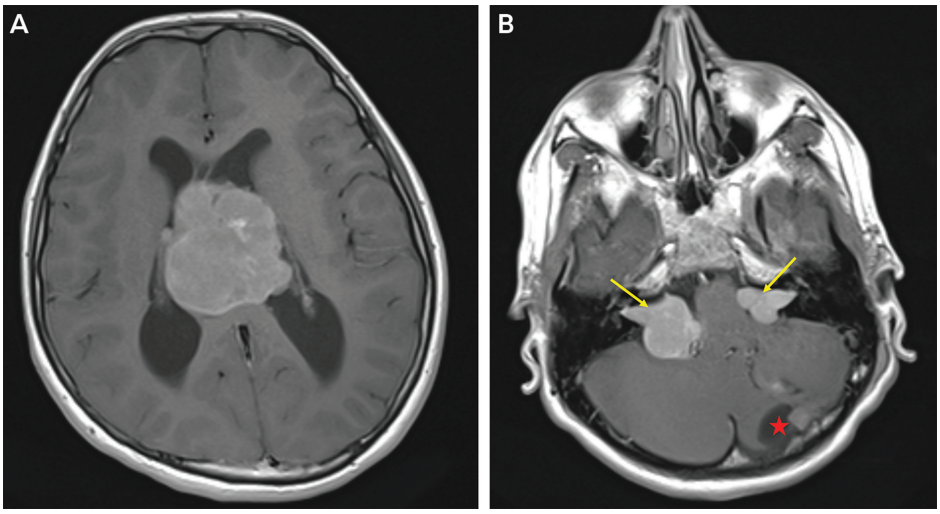

FIGURE 3-6

Imaging of the patient in CASE 3-3. *A*, Axial postcontrast T1-weighted MRI showing a large left lateral ventricle mass suggestive of meningioma. *B*, Axial postcontrast T1-weighted MRI showing bilateral vestibulocochlear schwannomas (*arrows*) and a cystic mass with small tentorial dural-based nodular thickening and masses suggestive of atypical features of meningioangiomatosis (*star*).

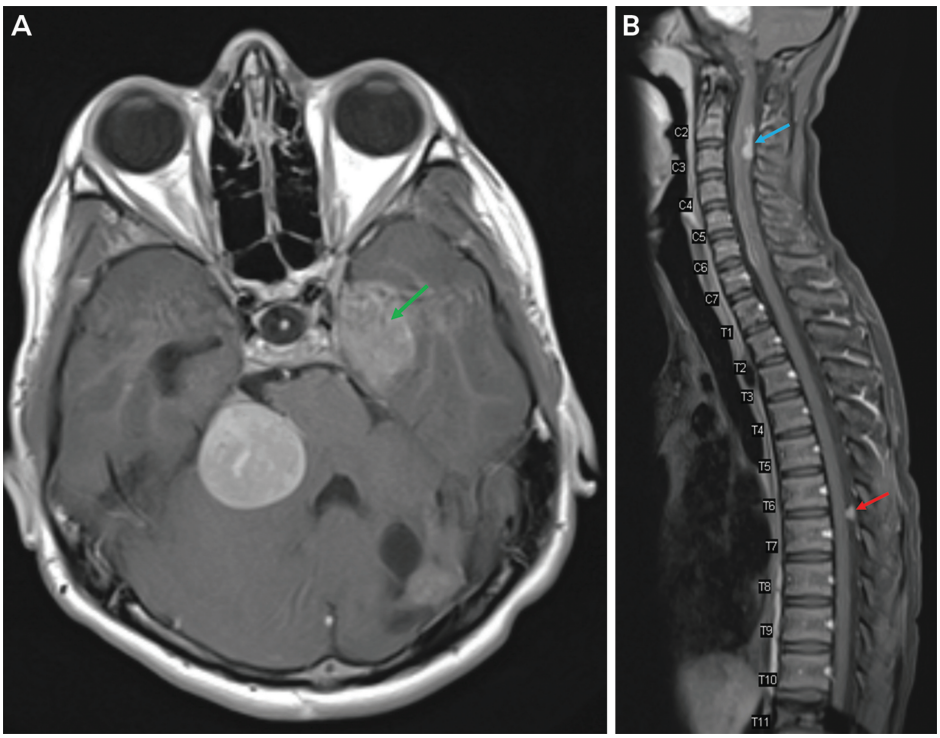

FIGURE 3-7

Imaging of the patient in CASE 3-3. *A*, Axial postcontrast T1-weighted MRI showing a left middle cranial fossa meningioma (*green arrow*). *B*, Sagittal postcontrast T1-weighted MRI of the spine showing an intramedullary mass at the C2 to C3 level likely representing an ependymoma (*blue arrow*) and a small meningioma in the right dorsal thecal sac at the T6 to T7 level (*red arrow*).

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and posterior fossa ependymoma group B are likely associated with a favorable prognosis.[45] Management is standardized for all tumor locations and includes maximal safe surgical resection followed by focal RT in children older than 1 year old. Craniospinal irradiation is recommended for patients with disseminated disease. Chemotherapy is currently used for children younger than 1 year old as a bridge to focal RT. A phase 3 study was completed to determine if chemotherapy provides any additional benefit after surgery; these data are currently being analyzed.[47] Recurrence in ependymomas is high and can occur up to 15 years after initial therapy.[46] For intracranial ependymomas in children, the 5-year overall survival is 70% and the 10-year overall survival is 52%.[45] Currently, treatment is not tailored to molecular subgroups but as clinical trials incorporate these data additional information will be acquired to allow for different treatment approaches.

Ependymomas can develop in 20% to 35% of patients with *NF2*-related schwannomatosis (NF2).[48] NF2-associated ependymomas are usually asymptomatic and can be multiple. Treatment is generally conservative; however, some patients require surgical intervention. NF2 is an autosomal dominant neurocutaneous condition with an incidence of 1 in 28,000; however, about 60% of patients with a de novo gene variation are found to have mosaicism (CASE 3-3).[48,49] Patients with NF2 are at an increased risk of developing other tumors including benign nerve sheath tumors (schwannomas), most often affecting the bilateral vestibular nerves (90%) but also other cranial, spinal, peripheral, and cutaneous nerves. Meningiomas can develop in 80% of patients with NF2. Meningioangiomatosis is a rare lesion seen in NF2 described as plaquelike leptomeningeal and perivascular proliferation of small blood vessels with calcifications.[50] Other neurologic manifestations include intracranial calcifications, cortical dysplasia, and neuropathy.[49,50] Ophthalmic findings in NF2 include lenticular opacities, epiretinal membranes, and retinal hamartomas. Cutaneous findings in NF2 include plaquelike dermal schwannomas associated with pigmentation, subcutaneous schwannomas, and café au lait macules (fewer in number than in NF1) (TABLE 3-3).[50]

CRANIOPHARYNGIOMAS

Craniopharyngiomas are rare tumors that arise in the suprasellar and intrasellar region, representing 2% to 6% of all pediatric brain tumors.[52] There are two histologic subtypes: adamantinomatous, which is more common in children, and papillary, which is frequently seen in adults. The peak age of incidence for adamantinomatous craniopharyngiomas in childhood and adolescence is 5 to 15 years (a bimodal peak with a second peak at 45 to 60 years). Pediatric patients will often present with visual disturbances, headaches, and endocrine deficiencies including short stature and delayed puberty. On MRI, adamantinomatous craniopharyngiomas are heterogeneous tumors composed of multiple cystic lesions, solid components, and calcifications. These tumors can be large, encase blood vessels, and adhere to adjacent structures. Histologically, adamantinomatous craniopharyngiomas have wet keratin nodules, stellate reticulum, and palisading epithelium.[52] Variations in *CTNNB1* are seen in adamantinomatous craniopharyngiomas. In addition, activation of the MAPK, immune, and inflammatory pathways have been observed as well.[53-55] Current treatment options for craniopharyngiomas include gross total resection or partial resection followed by focal RT. Both treatment options achieve comparable

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Revised Diagnostic Criteria for *NF2*-related Schwannomatosis, Formerly Known as NF2[a]

TABLE 3-3

A diagnosis of *NF2*-related schwannomatosis (previously termed neurofibromatosis 2, NF2) can be made when an individual has one of the following:

1 **Bilateral vestibular schwannomas**

2 **An identical *NF2* pathogenic variant in at least two anatomically distinct *NF2*-related tumors (schwannoma, meningioma, or ependymoma). (Note: If the variant allele fraction [VAF] in unaffected tissues such as blood is clearly <50%, the diagnosis is mosaic *NF2*-related schwannomatosis.)**

3 **Either two major or one major and two minor criteria as described in the following:**

Major criteria:

- Unilateral vestibular schwannoma
- First-degree relative other than sibling with *NF2*-related schwannomatosis
- Two or more meningiomas (Note: Single meningioma qualifies as minor criteria)
- *NF2* pathogenic variant[b] in an unaffected tissue such as blood (Note: If the VAF is clearly <50%, the diagnosis is mosaic *NF2*-related schwannomatosis.)

Minor criteria:

Can count >1 of a type (eg, two distinct schwannomas would count as two minor criteria)

- Ependymoma, meningioma (Note: Multiple meningiomas qualify as a major criteria), schwannoma (Note: If the major criterion is unilateral vestibular schwannoma, at least one schwannoma must be dermal in location)

Can count only once (eg, bilateral cortical cataracts count as a single minor criterion)

- Juvenile subcapsular or cortical cataract, retinal hamartoma, epiretinal membrane in a person aged <40 years, meningioma

Pattern of genetic changes in unaffected and tumor tissue in *NF2*-related schwannomatosis

Gene locus	Unaffected tissue[c]	Tumor 1	Tumor 2	Comment
NF2	PV1[d]	PV1	PV1	Shared *NF2* pathogenic variant
Allele 1	WT	LOH or	LOH or	Tumor-specific partial loss of 22q in trans position or a different *NF2* somatic second PV in every anatomically unrelated tumor
Allele 2		*NF2* PV2	*NF2* PV3	

LOH = loss of heterozygosity; NF2 = neurofibromatosis type 2; PV = pathogenic variant; WT = wildtype.
[a] Reprinted from Plotkin SR et al, Genet Med.[49] © 2017 Elsevier Ltd.
[b] If a likely pathogenic variant is identified, tumor analysis may aid upward classification to pathogenic variant.
[c] Tissues unaffected by tumors such as blood or skin.
[d] If the variant allele fraction is clearly <50%, the diagnosis is mosaic *NF2*-related schwannomatosis.

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results and decrease the risk of tumor recurrence; however, both are associated with significant morbidity and reduced quality of life. Overall survival at 5 years is 83% to 96% and at 10 years is 65% to 100%, with one-third of patients experiencing recurrence within 3 years of diagnosis.[52,56] Patients are at risk for visual impairment, panhypopituitarism, stroke, cognitive impairment, and hypothalamic injury syndromes including obesity, narcolepsy, mood disorders, and autonomic dysregulation. Mortality is also 3 to 5 times greater than in the general population due to long-term morbidity.[52] Intracystic therapy has been tried and is tolerable, although with limited tumor responses.[57,58] Surgical management of cysts including cyst aspiration is temporizing. Clinical trials using targeted therapy for MAPK, immune, and inflammatory pathways are currently ongoing with the goal of maintaining survival outcomes and minimizing morbidity.

GERM CELL TUMORS

CNS germ cell tumors represent 3% of all pediatric brain tumors and most commonly arise in the pineal and suprasellar regions.[59] One study found a significantly greater incidence of CNS germ cell tumors in patients of Asian descent than in individuals of other racial categories.[59] The incidence rate is highest for males 10 to 14 years old. Pineal tumors can cause obstructive hydrocephalus presenting with signs of increased intracranial pressure including vomiting, lethargy, and dorsal midbrain syndrome. Suprasellar tumors can present with endocrinopathies related to hypothalamic or pituitary dysfunction such as diabetes insipidus, delayed or precocious puberty, growth hormone deficiency, or vision impairment (eg, decreased visual acuity, bitemporal field deficits).

On imaging, CNS germ cell tumors are often midline and can present with multifocal or disseminated disease at the time of diagnosis. Therefore, a spine MRI is indicated. Germ cell tumors often have calcifications and cysts. On DWI, these hypercellular tumors can have restricted diffusion.[60] CNS germ cell tumors can be further classified into germinomas (55% to 65%) and nongerminomatous germ cell tumors (35% to 45%). Nongerminomatous germ cell tumors include embryonal carcinomas, yolk sac tumors, choriocarcinomas, teratomas (immature and mature), and mixed germ cell tumors. Tumor markers consisting of β-human chorionic gonadotropin (βHCG) and α-fetoprotein are evaluated in the serum and CSF as part of the diagnostic evaluation for germ cell tumors. Nongerminomatous germ cell tumors can secrete βHCG and α-fetoprotein, while germinomas can secrete βHCG only, although there is currently no consensus on what the upper limit for βHCG is for pure germinomas. Therefore, when tumor markers are inconclusive, a biopsy is recommended for diagnostic confirmation. The prognosis for patients with germ cell tumors is dependent on the subtype, with a more favorable prognosis for germinomas with a 10-year overall survival of 90%.[60,61] For patients with nongerminomatous germ cell tumors, the reported 5-year overall survival is 75% to 82%.[62]

Treatment for localized germinomas includes chemotherapy and RT involving the whole ventricles to prevent metastases. Treatment with craniospinal irradiation is indicated for patients with disseminated disease at diagnosis. Chemotherapy is given to reduce radiation dose in patients with localized germinomas, and surgery plays a limited role.[60] For nongerminomatous germ cell tumors, treatment consists of chemotherapy, surgery, and radiation. The

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goal of this combination approach is to achieve a complete response before receiving RT. Patients will receive four to six cycles of chemotherapy followed by second-look surgery before RT. The optimal dose and field of RT have not been identified but can include craniospinal irradiation for all patients or whole ventricular radiation for localized disease and craniospinal irradiation only for disseminated disease.[60,62] Molecular studies from a recent analysis of CNS germ cell tumors have identified MAPK and *PIK3CA*/mTOR pathway activity.[63] Current clinical trials for CNS germ cell tumors are directed at identifying the optimal RT plan for these patients.

LONG-TERM OUTCOMES AND NEUROTOXICITY FROM TREATMENT

Current standard treatment options for pediatric patients with brain tumors are associated with long-term neurologic toxicity and impairment in quality of life. With novel therapeutic approaches targeting the molecular biology of pediatric CNS tumors, the goal is to improve overall survival and decrease long-term morbidity for this patient population. This is discussed in more detail in the articles "Neurologic Complications of Conventional Chemotherapy and Radiation Therapy" by Jennie W. Taylor, MD, MPH,[64] and "Neurologic Complications of Cancer Immunotherapy" by Nancy Wang, MD, MPH,[65] in this issue of *Continuum*.

Chemotherapy

Chemotherapy for brain tumors can be associated with significant neurologic toxicity and long-term sequelae. Acute neurologic toxicity from chemotherapy includes encephalopathy, seizures, ataxia, and weakness. Vincristine, vinblastine, carboplatin, cyclophosphamide, cisplatin, ifosfamide, and etoposide are in chemotherapy regimens for pediatric CNS tumors. Vincristine and vinblastine can cause seizures and neuropathy while cisplatin and carboplatin can cause irreversible ototoxicity.[66] Hearing impairment can consequently cause issues with learning and development, especially in younger children. As such, clinical trials investigating agents for otoprotection are currently ongoing. Recently, the US Food and Drug Administration (FDA) approved sodium thiosulfate to reduce the risk of ototoxicity from cisplatin in pediatric patients with localized, nonmetastatic solid tumors.[67] Ifosfamide and etoposide can cause encephalopathy and agents such as methotrexate, cisplatin, vincristine, and bevacizumab can cause posterior reversible encephalopathy syndrome (PRES).[66]

Methotrexate, more commonly used in acute lymphoblastic leukemia, is sometimes given to infants with embryonal tumors and can cause acute encephalopathy, subacute toxicity presenting as strokelike symptoms, and chronic leukoencephalopathy.[68] Toxicity is more often associated with intrathecal administration and high doses in acute lymphoblastic leukemia regimens. With intrathecal administration, patients can develop aseptic meningitis. Acute encephalopathy occurs within 24 hours of administration and can present as altered mental status and seizures. Subacute encephalopathy can be mistaken for cerebral ischemia with transient focal neurologic deficits, typically 2 to 14 days after administration, and can last up to 72 hours before resolving spontaneously. On brain MRI, areas of restricted diffusion on DWI in multiple vascular territories can be seen, as well as nonenhancing T2 hyperintense white matter lesions. Leukoencephalopathy is present in 1 in 5 asymptomatic patients and all symptomatic patients with methotrexate

KEY POINTS

- Current treatment options for craniopharyngiomas include gross total resection or partial resection followed by focal radiation therapy. Both treatment options achieve comparable results and decrease the risk of tumor recurrence; however, both are associated with significant morbidity and reduced quality of life.
- Current standard treatment options for pediatric patients with brain tumors are associated with long-term neurologic toxicity and impaired quality of life.
- RT can cause acute and early-delayed neurotoxicity including headaches, pseudoprogression with worsening of preexisting neurologic symptoms, somnolence syndrome, and radiation necrosis, while late neurotoxicity includes radiation necrosis, neurocognitive impairment, vasculopathy, and secondary malignancies.
- Current recommendations for brain tumor survivors who have received RT include yearly neurologic examinations and brain MRI with diffusion-weighted imaging and MR angiography as clinically indicated.
- CNS tumor survivors should have yearly neuropsychological assessments to provide additional educational and school support as needed.

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toxicity.[68] Treatment includes leucovorin and supportive care. Most patients who have had methotrexate toxicity can receive subsequent doses without recurrence of symptoms.

Radiation Therapy

Radiation therapy can cause acute (days to weeks), early-delayed (first 6 months), and late (>6 months) neurotoxicity. Acute and early-delayed neurotoxicity includes headaches, pseudoprogression with worsening of preexisting neurologic symptoms, somnolence syndrome, and radiation necrosis, while late neurotoxicity comprises radiation necrosis, neurocognitive impairment, vasculopathy, and secondary malignancies like high-grade gliomas and meningiomas.[69] Somnolence syndrome is characterized by varying degrees of fatigue, irritability, nausea, vomiting, ataxia, headaches, and fever. Treatment is usually supportive, and corticosteroids and stimulants can sometimes help. The most common second malignancies post-RT are gliomas followed by meningiomas, with an increased risk at higher doses and younger age at the time of RT.[69,70] High-grade gliomas typically occur earlier with a median latency of 7 to 17 years, while meningiomas occur later with a median latency of 11 to 27 years.[69] Proton RT, a more precise delivery method, has been associated with improved cognitive outcomes although the risk of radiation necrosis, vasculopathy, and secondary malignancies remain unchanged.[70-73] Hall and colleagues[73] reported a 3-year cumulative risk of radiation-induced vasculopathy in patients with CNS or skull base tumors who received proton RT of 6.4%, with 2.6% of patients experiencing serious vasculopathy (ie, resulting in permanent neurologic deficits or requiring revascularization surgery). The Childhood Cancer Survivor Study[74] reported a cumulative incidence of 12% at 10 years, and Nordstrom and colleagues[75] reported a 5-year cumulative incidence of 5.4%. Stroke was reported in 1.2% of patients by Hall and colleagues,[73] 3.4% in the Childhood Cancer Survivor Study,[74] and 2% by Nordstrom and colleagues.[75] Data are limited for antithrombotic therapy for secondary stroke prevention in children and are mostly extrapolated from adults. Antiplatelet therapy is recommended for patients with moyamoya disease.[73,76,77] Surgical revascularization is considered in patients with clinical symptoms concerning for transient ischemic attacks or strokes, chronic subclinical ischemia, progressive vasculopathy, and high-grade vascular stenosis.[76,77] Current recommendations for brain tumor survivors who have received RT include yearly neurologic examinations and brain MRI with DWI and MR angiography (MRA) as clinically indicated.[78,79]

Radiation necrosis can be seen as early as immediately after completion of RT but can also present years later. The risk of radiation necrosis is greater with higher doses of radiation, concomitant use of certain chemotherapeutic agents, targeted therapy, radiosensitizers, and the modality of RT such as stereotactic radiosurgery.[80] While asymptomatic radiation necrosis can be managed with close observation, patients with symptomatic radiation necrosis, causing focal neurologic deficits, are treated with corticosteroids, bevacizumab (an antivascular endothelial growth factor monoclonal antibody), or both.[80,81]

Neurocognitive factors including attention, memory, and information processing are all negatively impacted in cancer survivors with CNS-directed therapy (eg, surgery, intrathecal chemotherapy, radiation), especially those who receive cranial RT.[82] Consequently, long-term health-related quality of life is

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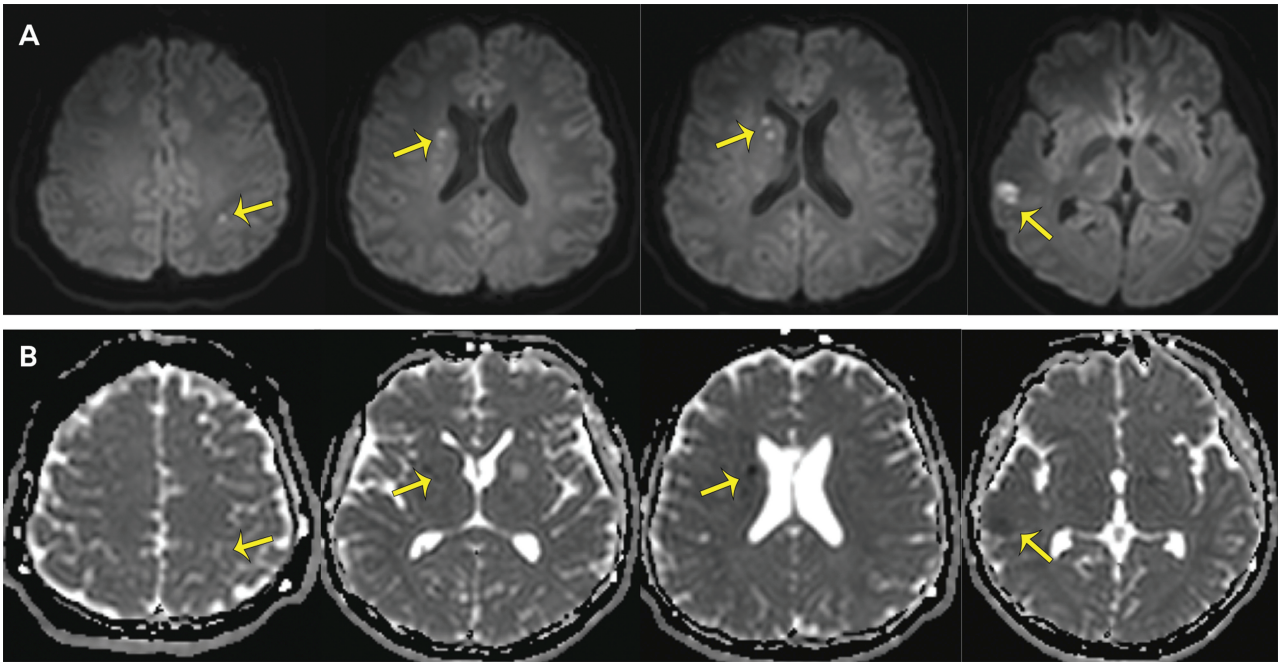

FIGURE 3-8
Imaging of a patient 2 years after completion of radiation therapy who presented with abrupt onset of generalized dyskinesia. Axial diffusion-weighted MRI (*A*) and axial apparent diffusion coefficient MRI (*B*) showing multifocal acute infarcts (*arrows*).

reduced as cognitive impairment can hinder education, employment, and social interactions.[83] Therefore, CNS tumor survivors should have yearly neuropsychological assessments to provide additional educational and school support as needed. Children are most vulnerable to RT-associated cognitive complications with the greatest risk during infancy to early childhood. Higher radiation doses, field (craniospinal irradiation), and photon therapy are all associated with the greatest risk of global neurocognitive impairment.[82] Clinical trials are underway to mitigate neurocognitive impairment from RT with pharmacotherapy and cognitive training. Metformin and memantine have been found to potentially improve cognitive function in adults and pediatric patients receiving RT.[84,85] A computerized training program for children who recently completed RT is being offered to help prevent memory and attention deficits.[86,87]

Vascular complications that can occur post-RT include cerebral microbleeds, cavernous malformations, and vasculopathy causing cerebral ischemia (FIGURE 3-8).[72,73,88] Cerebral microbleeds are RT-induced small vessel vasculopathies that are associated with poor executive function and working memory and cognitive decline.[89] Patients at greatest risk for developing cerebral microbleeds are those treated at a younger age and with higher doses and larger treatment volumes.[90] Other vascular malformations such as cerebral cavernous malformations can occur approximately 12 years post-RT and are most often asymptomatic, although patients can occasionally present with seizures, headaches, and focal neurologic deficits.[91] Surgical intervention may be considered for symptomatic lesions.

Strokelike migraine attacks after radiation therapy (SMART) syndrome is a rare late sequela of RT, occurring 1 to 40 years post-RT.[92] It is a reversible

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syndrome that can present with migrainelike headaches sometimes accompanied by focal neurologic deficits or seizures and lasting for several days to weeks. Most patients have complete resolution of their symptoms (80%); however, some may experience persistent neurologic deficits. On brain MRI with contrast, patients can have unilateral gyral hyperintensities involving the posterior aspect of the brain on fluid-attenuated inversion recovery (FLAIR) imaging, with corresponding gadolinium enhancement and cortical thickening. Treatment consists of managing symptoms.

Chimeric Antigen Receptor T-Cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy is currently being investigated for pediatric patients with brain tumors. Some targets include epidermal growth factor receptor variant III, GD2, B7-H3, and *HER2*.[93-97] Immunotherapy for CNS brain tumors can be associated with neurotoxicity including immune effector cell–associated neurotoxicity syndrome (ICANS) or tumor inflammation–associated neurotoxicity. Other side effects that can be seen are more systemic, such as cytokine release syndrome which typically occurs within the first week of therapy and can present with fever and multiorgan dysfunction. ICANS typically presents within 3 to 10 days of receiving CAR T-cell therapy and presents as encephalopathy.[98] Patients can present with confusion, word-finding difficulties, aphasia, impaired fine motor skills, tremors, and lethargy. In more severe cases, seizures, motor weakness, cerebral edema, increased intracranial pressure, and coma can occur. Patients at greatest risk for developing ICANS are those who have had severe cytokine release syndrome, preexisting neurologic comorbidities, high disease burden, and younger age.[98] Treatment for ICANS includes supportive care, steroids, and anakinra, an IL-1 receptor antagonist.[99,100] Patients with CNS tumors can develop tumor inflammation–associated neurotoxicity and neurologic symptoms related to CAR T-cell–mediated intratumoral inflammation.[97] These include worsening neurologic deficits and increased intracranial pressure. Treatment for tumor inflammation–associated neurotoxicity is similar to ICANS with supportive care, steroids, and anakinra. In patients with concerns for increased intracranial pressure and obstructive hydrocephalus, CSF removal via an Ommaya reservoir and IV hypertonic saline have been used.

CONCLUSION

Significant progress has occurred in the characterization of pediatric brain tumors and neurocutaneous syndromes using molecular diagnostics. This has allowed for a better understanding of the biology, management, risk stratification, and prognoses of these tumors and has led to novel therapeutic approaches targeting their biology. Advances in management have led to improved survival, but mortality remains high and significant morbidity persists. The goal of these novel therapeutic approaches is to improve overall survival and decrease the high risk of treatment-related morbidity. Being familiar with the most common pediatric CNS tumors and neurocutaneous conditions including a basic understanding of the biology, current management, and potential outcomes and morbidity is important in providing optimal neurologic care for this patient population. Long-term neurotoxicities continue to be a major concern and are being prioritized in many clinical trials to mitigate these

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complications and improve quality of life. Further understanding of the molecular diagnostics of pediatric CNS tumors will lead to continued refinement of tumor classification, management, and prognostication and will hopefully continue to improve the overall outlook for this patient population.

KEY POINT

- **Chimeric antigen receptor T-cell therapy for CNS brain tumors can be associated with neurotoxicity including immune effector cell–associated neurotoxicity syndrome or tumor inflammation–associated neurotoxicity.**

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Central Nervous System Lymphoma

By Lauren Schaff, MD

ABSTRACT

OBJECTIVE: **This article reviews the clinical presentation, diagnostic workup, staging, and treatment of primary central nervous system (CNS) lymphoma and common manifestations of secondary CNS lymphoma.**

LATEST DEVELOPMENTS: **Lymphoma can arise in the CNS de novo (primary CNS lymphoma) or as the result of systemic disease (secondary CNS lymphoma). Symptoms may include focal neurologic deficits related to the disease site, cognitive decline, and symptoms of increased intracranial pressure. Standard treatment may differ based on lymphoma subtype and location. A majority of CNS lymphoma is diffuse large B-cell subtype and exhibits aggressive behavior. First-line treatment is generally methotrexate-based polychemotherapy. Response rates to treatment are high, approximately 80% to 90% for primary CNS lymphoma, but relapse is common. Consolidation approaches including myeloablative chemotherapy followed by autologous stem cell rescue, nonmyeloablative chemotherapy, radiation, and medical maintenance regimens reduce rates of relapse. The recent development of targeted agents such as Bruton tyrosine kinase inhibitors and immunomodulatory strategies have shown promise in the treatment of CNS lymphoma. Immunotherapy in the form of checkpoint inhibitors and chimeric antigen receptor T cells is being studied. More indolent forms of lymphoma may be treated with radiation or targeted therapy.**

ESSENTIAL POINTS: **CNS lymphoma is an uncommon but clinically meaningful manifestation of extranodal lymphoma. The diagnosis requires a high level of suspicion for rapid initiation of potentially curative treatment.**

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RELATIONSHIP DISCLOSURE:
Dr Schaff has received personal compensation in the range of $500 to $4999 for serving as a consultant for Guidepoint and Ono Pharmaceutical Co., Ltd. and on a scientific advisory or data safety monitoring board for BTG International, Inc. An immediate family member of Dr Schaff has received personal compensation in the range of $500 to $4999 for serving as an expert witness for MichieHamlett Attorneys at Law. The institution of Dr Schaff has received research support from BTG International, Inc. and Merck & Co., Inc.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Schaff discusses the unlabeled/investigational use of chimeric antigen receptor T-cell therapy, ibrutinib, immune checkpoint inhibitors, lenalidomide, and temozolomide for the treatment of primary central nervous system lymphoma.

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INTRODUCTION

Lymphoma can arise in the central nervous system (CNS) either de novo (primary CNS lymphoma) or as the result of the spread of systemic disease (secondary CNS lymphoma). Almost any lymphoma subtype can affect the CNS, although diffuse large B-cell lymphoma is the most common. Most patients with CNS lymphoma have intraparenchymal brain disease, although rarely lymphoma can be isolated to the spinal cord, leptomeninges, vitreoretinal space, or dura. The neurologic presentation, treatment, and prognosis differ based on histology and the site of disease. Primary CNS lymphoma and aggressive forms of secondary CNS lymphoma can confer significant neurologic morbidity and mortality. Hematologic malignancies tend to be responsive to treatment, resulting in high rates of remission and

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symptom improvement. However, relapse is common, and long-term disease control is a challenge. This article reviews the clinical presentation, diagnosis, and treatment of primary CNS lymphoma and other hematologic malignancies involving the CNS. This article focuses on immunocompetent adult patients.

EPIDEMIOLOGY AND RISK FACTORS

CNS lymphoma affects approximately 0.45 per 100,000 individuals in the United States annually, accounting for 2% of all brain tumors.[1] Incidence increases with age, peaking at 2.5 per 100,000 in patients ranging from 75 to 84 years old.[2]

Immunosuppression is a risk factor for primary CNS lymphoma, particularly in patients with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) and those who have received organ transplants (posttransplant lymphoproliferative disease). CNS lymphoma in these settings is often associated with Epstein-Barr virus infection. Since the 1990s, the incidence of primary CNS lymphoma secondary to HIV or AIDS has decreased, while the incidence of primary CNS lymphoma in immunocompetent patients older than 65 years has increased.[3]

Secondary CNS involvement of systemic lymphoma frequently occurs at the time of lymphoma relapse and can affect up to 20% of patients with particularly aggressive subtypes such as Burkitt lymphoma.[4] Risk factors for CNS relapse include older age, poor performance status, elevated lactate dehydrogenase, high burden of systemic disease, and lymphomatous involvement of particular organs (eg, kidneys, adrenal glands, testes) or locations (eg, paranasal sinuses, retroperitoneal nodes). Patients with systemic lymphoma can be stratified by the CNS International Prognostic Index. The index accounts for risk factors including age greater than 60 years, elevated serum lactate dehydrogenase, poor performance status, stage 3 or 4 disease, the presence of more than one extranodal site of involvement, and the presence of renal or adrenal involvement. The index, validated in B-cell lymphoma, stratifies patients to low-risk (less than 1%), intermediate-risk (3%), and high-risk (greater than 10%) for CNS relapse within the first 2 years.[5] Patients with all six risk factors included in the CNS International Prognostic Index have a CNS relapse risk of approximately 33%.[5] Lymphomas with high-risk genetic features such as those harboring translocations of *MYC* and *BCL2* or *BCL6* also confer a higher risk of CNS relapse.[6,7]

CLINICAL PRESENTATION

Diagnosis of CNS lymphoma requires a high level of clinical suspicion because of its varied presentations. Generally, symptoms arise over weeks to months and vary based on the location of disease involvement. Approximately 70% of patients present with focal neurologic deficits[8] that may prompt imaging. However, 40% of patients present with nonspecific cognitive decline or behavioral changes that may initially be attributed to other causes, particularly in older patients.[8]

Focal peripheral nerve deficits may be a presenting symptom in patients with leptomeningeal involvement or direct nerve invasion (neurolymphomatosis). Leptomeningeal disease may be asymptomatic or can result in deficits of cranial nerves or symptoms localizing to the cauda equina, such as urinary retention or saddle anesthesia. Signs of increased intracranial pressure such as headache, nausea, and vomiting are also common. Neurolymphomatosis may present as a painful radiculopathy. Ocular involvement may be present in 25% of patients,

KEY POINTS

- Central nervous system (CNS) lymphoma involves the brain parenchyma, spinal cord, leptomeninges, dura, or vitreoretinal space without systemic involvement.
- The incidence of primary CNS lymphoma is increasing in immunocompetent patients more than 65 years old.
- Systemic lymphoma involving the kidneys, adrenal glands, testes, paranasal sinuses, or retroperitoneal lymph nodes have a higher risk of CNS relapse.
- Patients with CNS lymphoma can present with focal neurologic deficits or nonspecific cognitive decline or behavioral changes.
- Twenty-five percent of patients with CNS lymphoma may have ocular involvement at diagnosis. Slit-lamp examination should be performed for all patients.
- Classic radiographic findings of CNS lymphoma include homogeneous enhancement in immunocompetent patients, minimal edema, and diffusion restriction.
- CNS lymphoma in immunocompromised patients can demonstrate a ring-enhancing pattern.
- If CNS lymphoma is on the differential diagnosis, steroids should be withheld before tissue sampling. Lymphotoxic effects can obscure pathology results.

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although it is often asymptomatic, with only 4% of patients developing visual symptoms, generally described as blurred vision, decreased acuity, or floaters.[8,9]

DIAGNOSIS AND STAGING

Patients presenting with symptoms or findings concerning for CNS lymphoma should undergo brain imaging. MRI with a gadolinium-based contrast agent is the preferred modality. CNS lymphoma can present with a single lesion or be multifocal, and it is most often supratentorial.[8] Intraparenchymal disease is generally hypointense on T1-weighted and T2-weighted images, hyperintense on fluid-attenuated inversion recovery (FLAIR) images, and briskly enhancing following the administration of gadolinium contrast. In contrast to high-grade gliomas and solid tumor metastatic disease, enhancement in CNS lymphoma tends to be homogeneous, and there is often restricted diffusion. Edema may be present but is generally minimal relative to lesion size. Of note, CNS lymphoma may have a different radiographic appearance in patients who are immunocompromised, presenting as multifocal disease and demonstrating ringlike enhancement with central necrosis. A subset of patients may present with isolated leptomeningeal or vitreoretinal involvement, in which case brain MRI may be unremarkable. The diagnosis in these patients generally requires a high level of suspicion and necessitates lumbar puncture in patients suspected to have leptomeningeal disease and ocular slit-lamp examination in patients who may have vitreoretinal disease.

Pathologic confirmation is generally required for definitive diagnosis and usually necessitates an intracranial biopsy of a lymphomatous lesion. Whenever possible, steroids should be deferred in patients undergoing evaluation for CNS lymphoma because the lymphotoxic effects can obscure pathology results, leading to diagnostic delays. Extensive debulking is generally not pursued because of the infiltrative nature of the disease,[10] sensitivity to treatment obviating the need for aggressive surgery, and lack of clear survival benefit with resection in multiple retrospective studies.[8,11] For patients with leptomeningeal or ocular involvement, the diagnosis may be made via lumbar puncture or vitrectomy, respectively. When intraparenchymal lesions are present, brain biopsy should not be deferred in pursuit of a less invasive workup because this can introduce treatment delays. Given the potentially rapid nature of symptom progression, treatment initiation is urgent.

Differential Diagnosis

The differential diagnosis of CNS lymphoma depends on presentation. For patients with intraparenchymal disease, other primary or secondary CNS neoplasms are a common consideration. Diffusion restriction may raise the question of infarct. Tumefactive demyelination and inflammation may have a similar radiographic appearance. In patients who are immunosuppressed and have ring-enhancing brain lesions, infections such as toxoplasmosis or fungal abscesses are among the differential diagnoses. Ocular lymphoma can be mistaken for uveitis. CNS lymphoma may also appear similar to other cancer types, including ocular melanoma, leukemia, or other forms of lymphoma.

Staging

When CNS lymphoma is suspected or confirmed, patients must undergo staging to clarify the extent of the disease. To evaluate for a non-CNS systemic primary

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site, CNS lymphoma patients should have either positron emission tomography (PET) of the body or CT of the chest, abdomen, and pelvis, with a bone marrow biopsy. Male patients with CNS lymphoma should be evaluated for concurrent testicular lymphoma, either with PET of the body or dedicated testicular ultrasonography.

Full staging of the CNS is recommended to appropriately monitor treatment response. This includes MRI of the entire spine with and without gadolinium, lumbar puncture, and slit-lamp examination. CSF studies should include cell count, an evaluation of serum protein and glucose levels, cytology, and flow cytometry. Procedures recommended for diagnosis and staging are reviewed in TABLE 4-1.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Primary CNS lymphoma, by definition, is confined to the brain, spinal cord, leptomeninges, or vitreoretinal space. More than 90% of primary CNS lymphoma cases are diffuse large B-cell lymphoma, although primary forms of T-cell lymphoma, Burkitt lymphoma, and lower-grade lymphoproliferative diseases have also been described. Diffuse large B-cell lymphoma is further subcategorized as germinal center subtype or activated B-cell-like/nongerminal center subtype based on the expression of cellular markers. Approximately 75% of primary CNS lymphoma is considered activated B-cell-like/nongerminal center subtype subtype.[12] In systemic lymphoma, the activated B-cell-like/nongerminal center subtype confers a worse prognosis but prognostic significance in primary CNS lymphoma is unclear. The activated B-cell-like/nongerminal center subtype is associated with frequent mutations in the B cell

Work-up and Staging of Central Nervous System Lymphoma TABLE 4-1

Diagnostic work up (primary versus secondary)

- Positron emission tomography (PET) (chest, abdomen, pelvis)

OR

- CT (chest, abdomen, pelvis), bone marrow biopsy, and testicular ultrasonography (male patients)

Central nervous system staging

- Brain MRI with and without gadolinium
- Spine MRI with and without gadolinium
- Lumbar puncture (CSF analysis of total cell count, protein, glucose, flow cytometry, and cytology)
- Ocular slit-lamp examination

Prognostic factors

- Age
- Performance status (Karnofsky Performance Status Scale or Eastern Cooperative Oncology Group Performance Status Scale)
- Human immunodeficiency virus (HIV) status

CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging.

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receptor pathway, which has led to the recent development of targeted therapeutic strategies.

Treatment of primary CNS lymphoma is time sensitive and should be initiated as soon as it is diagnosed; common practice is to initiate treatment immediately after diagnosis, without an intervening hospital discharge. There are generally two phases of primary CNS lymphoma treatment: (1) induction therapy and (2) consolidation or maintenance therapy. The purpose of induction is to reduce gross disease, whereas consolidation eliminates residual, sometimes microscopic, disease, with the goal of durable remission or cure.[13] A maintenance strategy is sometimes selected over consolidation and implies ongoing, generally low-dose treatment to prolong remission.

Induction Therapy

Until the 1980s, the first-line treatment for primary CNS lymphoma was whole-brain radiation therapy. Despite high rates of radiographic and clinical response, durable benefit was not achieved, and overall survival time ranged between 12 and 18 months.[14,15] Typical chemotherapeutic regimens used for systemic lymphoma, such as cyclophosphamide, doxorubicin, vincristine, and prednisone, did not confer a survival benefit in primary CNS lymphoma, likely because of poor penetrance of the blood-brain barrier. High doses of methotrexate, a folate antimetabolite that impairs DNA synthesis, penetrate the CNS and improve overall survival compared with whole-brain radiation therapy alone. The addition of cytarabine to methotrexate resulted in an improvement in overall response rate from 40% to 69% in a randomized clinical trial,[16] setting the stage for polychemotherapeutic regimens with a methotrexate backbone.

Several methotrexate-based regimens have emerged over the years, largely supported by single-arm phase 2 studies demonstrating similar response rates and survival. Because of the rarity of primary CNS lymphoma, there are few head-to-head clinical trials. One randomized phase 2 study in patients 60 years old and older compared methotrexate, vincristine, and procarbazine followed by cytarabine with methotrexate and temozolomide. Overall response rates (82% versus 71%) and overall survival times (31 versus 14 months) favored the methotrexate, vincristine, and procarbazine arm without a difference in toxicity, but the response differences between groups were not statistically significant.[17] The International Extranodal Lymphoma Study Group-32 (IELSG32) trial compared (1) methotrexate and cytarabine, (2) methotrexate, cytarabine, and rituximab, and (3) methotrexate, cytarabine, rituximab, and thiotepa.[18] While patients in the methotrexate, cytarabine, rituximab, and thiotepa arm had the best overall response rate and progression-free survival in the trial, outcomes were not clearly better than historical controls. Ultimately, the superiority of one regimen over another has not been established. As such, regimens often vary by institutional and practitioner preference. The optimal dose of methotrexate is also not clear and the dose varies between regimens. Generally, doses of 3 g/m^2 or greater are thought to be effective. It is unknown whether there is a benefit to higher doses of methotrexate (8 g/m^2).

Methotrexate is generally well tolerated, although it can be associated with acute kidney injury, which in turn results in delayed methotrexate clearance and further toxicity. Toxic methotrexate levels can result in end-organ damage, including mucositis, pneumonitis, hepatitis, and bone marrow suppression.

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Rarely, methotrexate can be associated with neurotoxicity and strokelike symptoms. To prevent toxicity and facilitate methotrexate clearance, patients are generally admitted for continuous IV hydration and monitoring until clearance is documented. Leucovorin is administered to protect systemic tissue from methotrexate effects. Glucarpidase is a bacterial recombinant enzyme that rapidly cleaves methotrexate to inactive byproducts and is approved by the US Food and Drug Administration (FDA) as a treatment for methotrexate toxicity. Given the efficacy of methotrexate-based therapy for primary CNS lymphoma and the general tolerability, treatment with methotrexate is recommended even in older patients.

Rituximab, an anti-CD20 monoclonal antibody, is frequently incorporated into treatment regimens targeting B-cell lymphoma. The IELSG32 trial demonstrated improved response when rituximab was added to methotrexate and cytarabine (74% versus 53%);[18] however, the role of rituximab was recently called into question by a phase 3 clinical trial that did not suggest a survival benefit with the addition of rituximab to methotrexate, teniposide, carmustine (BCNU), and prednisone.[19] Regardless, many providers continue to include rituximab based on IELSG32 data as well as multiple retrospective studies supporting its use and general tolerability.

Overall, methotrexate-based therapy leads to radiographic response rates in 80% to 90% of patients (CASE 4-1), allowing many to proceed with potentially curative consolidation therapy.

Site-specific Treatment

The role of site-specific therapy for patients with leptomeningeal or ocular involvement of primary CNS lymphoma remains controversial. High-dose IV methotrexate achieves cytotoxic concentrations in the CSF[20] and vitreous space,[21] obviating the need for direct intrathecal or intraocular administration. Increasingly, many practitioners reserve intrathecal chemotherapy for persistent or refractory leptomeningeal disease. Common intrathecal therapeutic agents include methotrexate, rituximab, cytarabine, and thiotepa. Intrathecal chemotherapy can be administered via lumbar puncture or, preferentially, an Ommaya reservoir which provides better distribution. Disease of the vitreoretinal space is often similarly addressed first with systemic methotrexate-based regimens.[22] For patients with primary vitreoretinal lymphoma and no evidence of disease in the brain parenchyma, site-directed therapy could be considered in the form of intravitreal chemotherapy (most commonly rituximab or methotrexate) or ocular radiation.[23] These local therapies may also be used in the event of persistent ocular disease after methotrexate.

Consolidation Therapy

Despite initial responses to high-dose methotrexate, primary CNS lymphoma relapse is seen in more than 50% of patients. Consolidation regimens appear to reduce the risk of relapse and can include high-dose myeloablative chemotherapy followed by autologous stem cell transplant, high-dose nonmyeloablative chemotherapy, or whole-brain radiation therapy. Maintenance strategies, instead of consolidation, may also be appropriate for some patients.

Increasingly, high-dose myeloablative chemotherapy followed by autologous stem cell transplant is the preferred consolidation strategy for patients able to

KEY POINTS

- Aggressive surgical resection of CNS lymphoma is not associated with a survival benefit.
- Diffuse large B-cell lymphoma is the most common form of primary CNS lymphoma. Most primary CNS lymphomas are of the activated B-cell-like/nongerminal center subtype and are associated with mutations in the B-cell receptor pathway.
- Initiation of primary CNS lymphoma treatment is time-sensitive. Common practice is to begin treatment immediately after diagnosis, without an intervening hospital discharge.
- There are two phases of primary CNS lymphoma treatment: (1) induction and (2) consolidation or maintenance.
- Chemotherapeutic regimens used for systemic lymphoma generally have poor penetrance of the blood-brain barrier and are not effective for primary CNS lymphoma.
- Polychemotherapy regimens with a methotrexate backbone are first-line treatments for primary CNS lymphoma.
- Methotrexate is well tolerated and elicits responses in 80% to 90% of patients with CNS lymphoma. Tumor-directed treatment is recommended even in older patients.

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CASE 4-1

A 68-year-old man presented to a local hospital with several days of erratic behavior followed by 2 days of increased somnolence. Brain MRI revealed multiple homogeneously enhancing lesions with restricted diffusion and minimal mass effect (FIGURE 4-1A, 4-1B, and 4-1C). Lymphoma was suspected based on radiographic appearance, and steroids were withheld. A CT of his chest, abdomen, and pelvis and testicular ultrasonography were performed and did not reveal systemic disease. The patient underwent a stereotactic biopsy, and the pathology was consistent with diffuse large activated B-cell-like/nongerminal center subtype lymphoma. Bone marrow biopsy, CSF sampling, and ocular slit-lamp examination results were negative for lymphoma. The patient was treated with high-dose methotrexate in combination with rituximab, vincristine, and procarbazine. Brain MRI after four doses of methotrexate demonstrated a near-complete response (FIGURE 4-1D), and he returned to his cognitive baseline. Complete radiographic response was achieved after an additional four doses of methotrexate, and the patient was consolidated with autologous stem cell transplantation with a thiotepa, busulfan, and cyclophosphamide conditioning regimen. He remained in remission for more than 5 years after completion of therapy.

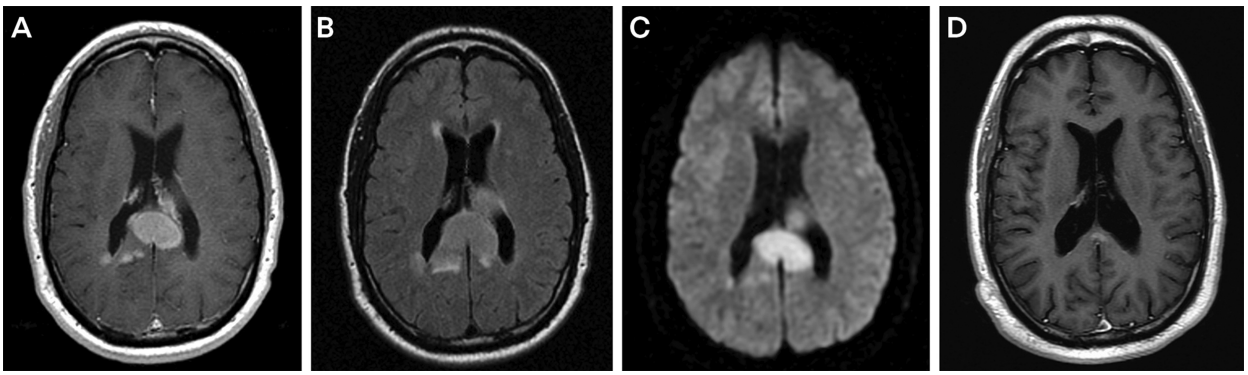

FIGURE 4-1
Characteristic MRI features of primary central nervous system lymphoma as represented by the patient in CASE 4-1. *A*, Axial gadolinium-enhanced T1-weighted image with characteristic homogeneously enhancing corpus callosal lesions. *B*, Axial fluid-attenuated inversion recovery (FLAIR) image demonstrating minimal surrounding edema. *C*, Axial diffusion-weighted image demonstrating restricted diffusion in the lesion. *D*, Axial gadolinium-enhanced T1-weighted image after four doses of high-dose IV methotrexate reveals near-complete treatment response.

COMMENT

This case illustrates a typical presentation of primary central nervous system lymphoma with characteristic imaging features. It demonstrates the evaluations required for staging and first-line therapy in a patient who is eligible for an autologous stem cell transplant.

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tolerate this treatment; generally, this includes patients who are younger than 70 years old, can independently perform activities of daily living, and have few medical comorbidities. Long-term data from the randomized phase 2 Cranial Radiotherapy or Intensive Chemotherapy With Hematopoietic Stem Cell Rescue for Primary Central Nervous System Lymphoma in Young Patients (PRECIS) study compared consolidative high-dose myeloablative chemotherapy followed by autologous stem cell transplant to 40 Gy of whole-brain radiation therapy and reported 8-year event-free survival in 67% of patients who received autologous stem cell transplants versus 39% of those consolidated with whole-brain radiation therapy.[24] However, overall survival was not significantly different (69% versus 65%). Notably, balance and neurocognition were markedly worse in the group who received whole-brain radiation therapy.[24] The choice of chemotherapeutic conditioning regimen is likely important, with single-arm and retrospective studies favoring thiotepa, busulfan, and cyclophosphamide or carmustine (BCNU) and thiotepa more than the carmustine (BCNU), etoposide, cytarabine, and melphalan regimen, commonly used for systemic lymphoma.[25]

For patients unable or unwilling to undergo high-dose myeloablative chemotherapy followed by autologous stem cell transplant, nonmyeloablative cytarabine with or without etoposide may be administered for consolidation.[26] Although whole-brain radiation therapy has historically been a common method of consolidation, neurotoxicity with the standard 40 Gy dose is increasingly recognized. Some studies have used lower doses in an attempt to minimize toxicity. A study of methotrexate-based induction followed by cytarabine or cytarabine plus whole-brain radiation therapy of 23.4 Gy demonstrated improved progression-free survival with the addition of whole-brain radiation therapy. Longer follow-up is required to determine if there is a difference in overall survival.[27] The impact on neurotoxicity is not yet known as data from neuropsychological testing has not yet been reported.

Maintenance strategies may offer another alternative to consolidation. Temozolomide, rituximab, and methotrexate have been used in this setting, although a recent phase 3 study did not demonstrate improved outcomes when maintenance temozolomide was added to whole-brain radiation therapy consolidation.[28] Several single-arm clinical trials have explored the use of targeted therapies as maintenance strategies, including the Bruton tyrosine kinase inhibitor ibrutinib and the immunomodulating agent lenalidomide.[13]

Monitoring

Upon completion of treatment, patients must be monitored closely for evidence of relapse. Guidelines set by the National Comprehensive Cancer Network recommend repeat MRI every 3 months for the first 2 years, followed by every 6 months for another 3 years, and then annually.[29] Late relapses (after more than 10 years) have been reported, so many practitioners monitor patients indefinitely.

Relapsed and Refractory Disease

Primary CNS lymphoma recurs in more than 50% of patients and is refractory to methotrexate-based treatment in another 10% to 15% of patients. At the time of relapse, restaging should be performed, including body imaging, because primary CNS lymphoma can rarely relapse systemically.

KEY POINTS

- The role of intrathecal and intraocular chemotherapy as site-specific treatments for patients with lymphoma is controversial. These therapies may be reserved for methotrexate failure.
- In patients with primary CNS lymphoma, high-dose chemotherapy with thiotepa, busulfan, and cyclophosphamide followed by autologous stem cell rescue is the preferred consolidation strategy. Eligible patients are typically younger than 70 years and in good general health.
- Maintenance treatment may be a reasonable alternative to consolidation treatment for patients with primary CNS lymphoma.
- After primary CNS lymphoma treatment, patients should be monitored with imaging every 3 months for the first 2 years, then every 6 months for an additional 3 years, and then annually.
- Primary CNS lymphoma relapse occurs in up to 50% of patients.
- Rechallenge with methotrexate-based chemotherapy is reasonable for patients with relapse of primary CNS lymphoma who had an initial response to methotrexate that lasted 12 months or longer.
- Ibrutinib, a Bruton tyrosine kinase inhibitor, is highly effective in treating relapsed and refractory primary CNS lymphoma. It may be used in combination with other agents to prevent resistance.

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There is no standard approach to treatment of relapsed or refractory primary CNS lymphoma. Prognosis is generally considered poor with an estimated survival time of 3.7 months for patients with relapsed disease and 2 months for patients refractory to methotrexate,[30] though newer therapies such as ibrutinib may improve these outcomes. Methotrexate rechallenge is a reasonable approach for patients with an initial response to methotrexate, particularly in patients whose initial response lasted 12 months or longer.[31] Other strategies include alternative chemotherapeutic regimens, targeted therapies, immunomodulators, or immunotherapy. Ibrutinib is an oral Bruton tyrosine kinase inhibitor that targets the B-cell receptor pathway, commonly activated in primary CNS lymphoma. Treatment with ibrutinib induces response in up to 90% of patients[32,33] but development of resistance is a challenge with a progression-free survival time of 4 to 8 months with ibrutinib monotherapy.[32] As a result, ibrutinib is often used in combination with methotrexate and rituximab.[29] Studies of other combination strategies are ongoing in an effort to prolong progression-free survival. Ibrutinib can confer an increased risk of aspergillosis, and patients should be monitored carefully.

Immunomodulators such as lenalidomide have also been effective in the relapsed or refractory setting.[34] Immunotherapy with checkpoint inhibition has elicited responses in some patients.[35,36] Patients with a response to second-line therapy may be candidates for high-dose myeloablative chemotherapy followed by autologous stem cell transplant, and second transplants can be performed. Whole-brain radiation therapy is often reserved for the relapsed or refractory setting.

Of increasing interest is the potential role of chimeric antigen receptor (CAR) T-cell therapy in patients with primary CNS lymphoma. These are T cells that are genetically engineered to target CD19, which is expressed on lymphoma cells. This therapy is approved for use in patients with systemic lymphoma relapse and CNS involvement. Studies are ongoing in the primary CNS lymphoma population and appear promising.[37,38]

CNS INVOLVEMENT OF SYSTEMIC HEMATOLOGIC MALIGNANCIES

CNS involvement of systemic lymphoma is thought to occur via several mechanisms: hematologic spread, direct extension from adjacent bone marrow, or centripetal growth along neurovascular bundles. Overall, this is a rare complication of systemic lymphoma, affecting up to 5% of patients.[5] However, rates are significantly higher in certain high-risk groups. Patients considered at high risk of CNS involvement, such as those with Burkitt or primary testicular lymphoma or otherwise high CNS International Prognostic Index scores, may receive CNS-directed prophylaxis in the form of intrathecal or intravenous high-dose methotrexate. Intravenous high-dose methotrexate may be more effective than intrathecal administration at reducing the risk of relapse.[39] The practice is more controversial in intermediate and low-risk patients.

Patients with secondary CNS lymphoma may present similarly to patients with primary CNS lymphoma; however, the leptomeninges are a more common site of disease than the intraparenchymal compartment. CNS relapse is generally associated with aggressive disease and survival has typically been considered poor, though recent therapeutic developments discussed elsewhere in this article (e.g. targeted treatment, immunotherapy) are improving outcomes.

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Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma can present in the CNS synchronous with systemic disease or as an isolated site of relapse. Standard treatments for diffuse large B-cell lymphoma do not have CNS penetrance. As a result, treatment of synchronous disease generally involves the incorporation of high-dose methotrexate to standard diffuse large B-cell lymphoma treatment regimens such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. Patients may undergo thiotepa-based autologous transplant if they can tolerate or alternate consolidative regimens. Treatment of isolated CNS relapse is generally extrapolated from the primary CNS lymphoma literature and involves methotrexate-based combination regimens as previously described (CASE 4-2).

CAR T-cell therapy is a potential treatment option for relapsed diffuse large B-cell lymphoma involving the CNS. A prospective study of lisocabtagene maraleucel was the first to enroll patients with lymphomatous involvement of the CNS, and it demonstrated complete response in three of six evaluable patients, with acceptable toxicity.[40] Retrospective data with other CAR T-cell products suggest similar rates of efficacy.[41,42]

Other B-Cell Histologies

CNS involvement of more indolent B-cell subtypes, such as chronic lymphocytic leukemia, mantle cell lymphoma, and lymphoplasmacytic lymphoma, is rare but does occur. CNS involvement (usually leptomeningeal) by Waldenström macroglobulinemia is termed Bing-Neel syndrome. The advent of the Bruton tyrosine kinase inhibitor ibrutinib has changed the approach to these diseases because dramatic and sustained responses are common. For patients who progress on Bruton tyrosine kinase inhibition, venetoclax, a BCL2 inhibitor, may be used. Lenalidomide is another treatment option. Methotrexate can also be used in refractory settings or to assist with disease control in patients who are severely symptomatic. As with primary CNS lymphoma, the utility of intrathecal chemotherapy is unclear, but intrathecal methotrexate, cytarabine, or rituximab could be considered if CSF cytology is persistently positive.

Natural Killer/T-Cell Lymphoma

Natural killer/T-cell lymphomas represent a heterogeneous group of lymphoid neoplasms, with more than 30 subtypes recognized in the 5th edition of the World Health Organization Classification of Haematolymphoid Tumors.[43] These represent a rare group of malignancies that affect the CNS either de novo (representing 2% of primary CNS lymphoma cases) or, more commonly, as a site of relapse. Risk factors for CNS involvement are similar to those of B-cell lymphoma and include elevated lactate dehydrogenase, gastrointestinal involvement, involvement of more than one extranodal site, and involvement of paranasal sinuses. There appears to be a slight predominance of natural killer/T-cell lymphomas in men versus women. The prognosis of natural killer/T-cell lymphoma with CNS involvement is poor and the median overall survival time is often less than 3 months.[44] There is no standard treatment, and many oncologists will use MTX-based combination chemotherapy. Rituximab is omitted in the treatment of natural killer/T-cell lymphoma because CD20 is not expressed. Retrospective evidence suggests PD-1 inhibition may play a role in the treatment of extranodal natural killer/T-cell lymphoma.[45,46]

KEY POINTS

- Secondary central nervous system involvement of systemic lymphoma can occur by hematologic spread, direct extension, or growth along neurovascular bundles.
- Methotrexate-based treatment is first-line therapy for secondary CNS diffuse large B-cell lymphoma.
- Patients with secondary CNS lymphoma may be eligible for chimeric antigen receptor T-cell therapy.
- CNS involvement of more indolent forms of B-cell lymphoma is rare, and it is often responsive to Bruton tyrosine kinase inhibition.

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CASE 4-2

A 57-year-old man with a history of stage IV diffuse large B-cell lymphoma thought to be in remission after multiple lines of therapy, most recently tisagenlecleucel chimeric antigen receptor T-cell therapy, developed slurred speech and aphasia over 4 days. Brain MRI on presentation revealed diffusion-restricting, enhancing lesions in his left frontal lobe (FIGURE 4-2A).

Intracranial biopsy was deferred because of high suspicion for lymphoma. CSF revealed an abnormal B-cell population consistent with lymphoma. The patient received high-dose methotrexate and had rapid improvement of his symptoms, which corresponded with the radiographic response (FIGURE 4-2B). After five doses of methotrexate, he was transitioned to ibrutinib maintenance and remained stable for 18 months.

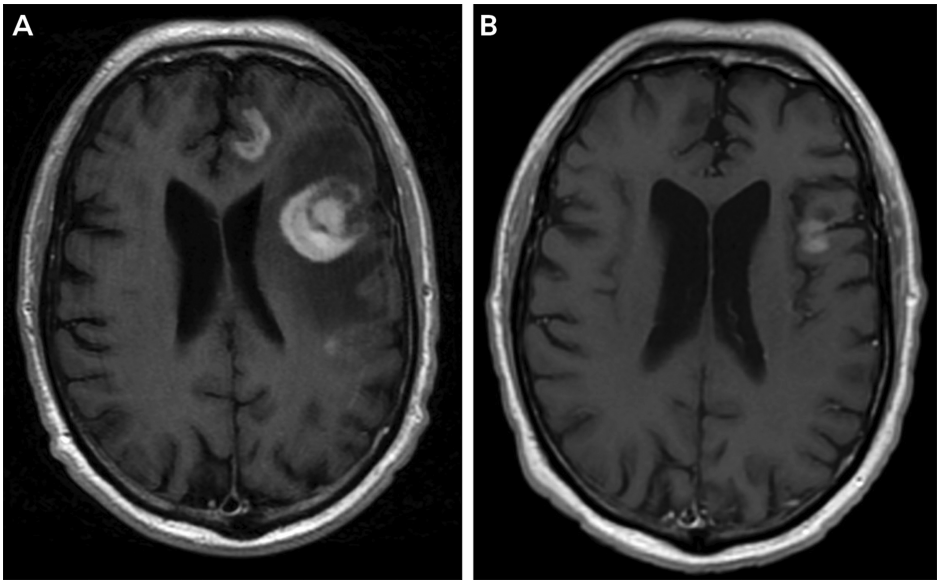

FIGURE 4-2
Brain MRI of the patient in CASE 4-2 with secondary central nervous system lymphoma. *A*, Axial gadolinium-enhanced T1-weighted image demonstrating two left frontal enhancing lesions. *B*, Follow-up gadolinium-enhanced T1-weighted axial MRI after five doses of methotrexate and initiation of ibrutinib maintenance reveals near-complete treatment response.

COMMENT

This case demonstrates that high-dose methotrexate can elicit responses even in heavily pretreated patients. The case also illustrates that maintenance therapy is a treatment option instead of consolidation, and it highlights the potential role of novel targeted therapies.

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Site-specific Considerations

Lymphoma can present isolated to or involving specific locations that may predict symptomatology or natural history and dictate treatment.

DURAL LYMPHOMA. Primary dural lymphoma describes lymphoma isolated to the dura mater without evidence of other systemic involvement. Common presenting features include headache, seizure, and focal neurologic deficits.[47] Imaging reveals single or multiple enhancing dural lesions (CASE 4-3), and findings may be mistaken for meningioma. Pathologic sampling often reveals a marginal-zone lymphoma, although follicular lymphoma and higher-grade lymphomas have also been reported. Full systemic and CNS staging is required. More than 25% of patients with marginal-zone lymphoma have stage IV disease at diagnosis, and involvement of the leptomeningeal space is common. Dural lymphoma is frequently indolent, and treatment is typically effective.[48] If complete surgical resection is achieved, patients may be monitored radiographically. If not, involved-field low-dose radiation therapy is recommended and can result in durable response. Chemotherapy is generally reserved for recurrence.

NEUROLYMPHOMATOSIS. Neurolymphomatosis is the direct lymphomatous invasion of a peripheral or cranial nerve. This is often a manifestation of relapse, but it can present as the primary site of disease. As with many other lymphomas, B-cell involvement is the most common in histology, although T-cell involvement has been described.

Clinically, patients often experience a painful radiculopathy, although involvement can be painless. MR imaging may reveal enlarged and enhancing nerves. Systemic PET may also help visualize involved nerves. For cases in which the diagnosis is in question, a biopsy may be required and should reveal lymphomatous nerve invasion. Treatment is generally methotrexate-based therapy.

INTRAVASCULAR LYMPHOMA. Intravascular lymphoma is a rare manifestation of lymphoma. It is defined by the proliferation of lymphoma cells isolated to the lumen of capillaries and postcapillary venules. Symptoms are generally end-organ dysfunction caused by vessel occlusion. Skin lesions are common. Neurologically, patients may experience a rapid form of dementia, progressive strokes, or peripheral neuropathy. B symptoms such as night sweats, fever, and weight loss, may also be seen. The diagnosis requires a high degree of suspicion and is often confirmed via biopsy of skin lesions. If skin lesions are not present, biopsies of normal skin tissue can be considered. Biopsies should be excisional and include subcutaneous fat to maximize yield. Intravascular lymphoma is most commonly of the diffuse large B-cell subtype and can be treated with typical systemic therapy such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. In cases of CNS involvement, methotrexate should be used.

PROGNOSIS AND SURVIVORSHIP

CNS lymphoma is highly chemosensitive and radiosensitive and tumor-directed therapy often results in improved symptoms. For this reason, even patients with high symptom burden or poor performance status due to disease should be treated aggressively.

KEY POINTS

- CNS involvement of T-cell lymphomas is rare but confers a poor prognosis.
- Dural lymphoma is often indolent and may be treated with surgical resection or radiation with excellent response.
- Neurolymphomatosis often presents as a painful radiculopathy.
- Neurologic manifestations of intravascular lymphoma include strokes, peripheral neuropathy, and rapid-onset dementia. The diagnosis requires a biopsy.

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Currently, the prognosis may be predicted by two models: (1) the prognostic model for primary CNS lymphoma based on data from the IELSG32 study, which includes age, performance status, measurement of lactate dehydrogenase, involvement of deep brain structures, and CSF protein concentration,[49] and (2) the Memorial Sloan Kettering Cancer Center prognostic model (primary CNS lymphoma and secondary CNS lymphoma),[50] which incorporates age and functional status.[51]

The overall survival of patients with primary CNS lymphoma has improved in the last several decades from 12.5 months, before the widespread use of methotrexate, to 26 months in the 2010s.[52] Likely, these outcomes will continue

CASE 4-3

A 56-year-old woman developed sudden-onset numbness of her right face and arm, lasting 5 minutes. She was unable to speak during the episode. Brain MRI revealed a dural mass overlying her left frontal lobe that was approximately 1.5 cm thick. Dural thickening extended over her left frontal convexity to involve her anterior falx (FIGURE 4-3A). Positron emission tomography (PET) of her body was negative for systemic malignancy. A lumbar puncture was also negative for disease. She underwent a left-sided craniotomy for debulking. Pathology revealed a low-grade B-cell lymphoma with plasmacytic differentiation, consistent with a marginal-zone lymphoma. She was treated with radiation therapy, 28 Gy in 14 fractions. Follow-up imaging demonstrated interval resolution of residual dural enhancement (FIGURE 4-3B).

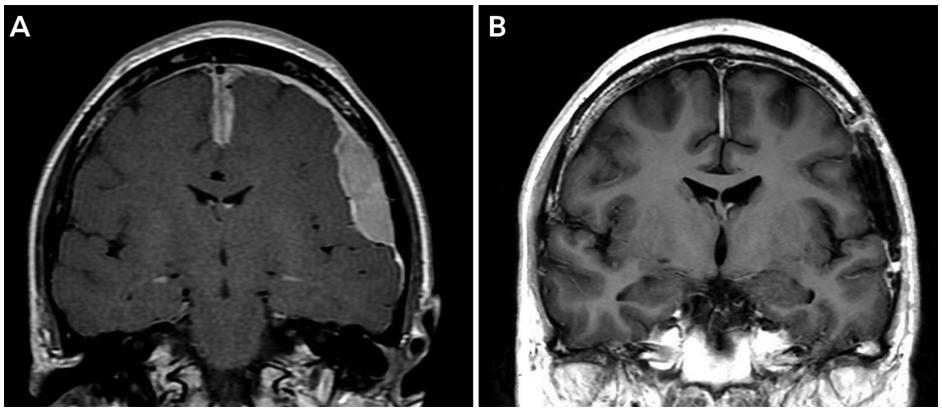

FIGURE 4-3
Brain MRI of the patient in CASE 4-3 with dural lymphoma. *A*, Coronal gadolinium-enhanced T1-weighted image with left frontal dural mass and extensive dural thickening involving the anterior falx. *B*, Coronal gadolinium-enhanced image after resection of the mass and radiation treatment revealing radiographic response.

COMMENT

This case provides an example of dural lymphoma and treatment response to low-dose radiation therapy.

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to improve with increased use of high-dose myeloablative chemotherapy followed by autologous stem cell transplant consolidation and the success of newer therapeutic strategies such as ibrutinib.

As survival improves, quality of life after treatment is of increasing importance. Generally, induction chemotherapy results in an improvement in cognitive domains and health-related quality of life as tumor symptoms abate.[53] However, in one study of 23 patients with primary CNS lymphoma who were treated with methotrexate-based chemotherapy alone, 48% displayed at least mild cognitive deficits at long-term follow-up, and 17% reported diminished quality of life. Only 7 of 11 patients returned to work in some capacity after primary CNS lymphoma remission.[54] Similarly, responses to the European Organisation for Research and Treatment Core Quality of Life questionnaire showed deterioration in social functioning over time after treatment with IV and intrathecal chemotherapy.[55] It is unclear whether these effects are residual deficits from tumors or consequences of chemotherapy.

Use of whole-brain radiation therapy at doses of 36 Gy or greater is associated with neurotoxicity, specifically impaired attentiveness and executive function,[56–58] and whole-brain radiation therapy has generally fallen out of favor as a first-line treatment. As previously discussed, the long-term effect of lower radiation therapy doses (23.4 Gy) is less clear. Longer-term follow-up of high-dose myeloablative chemotherapy followed by autologous stem cell transplant is needed, but early data suggest cognitive function is better preserved.

One thing that is clear is that as new therapeutics are developed, the assessment of long-term effects on quality of life and neurocognitive functioning is crucial. Patient-reported outcomes and cognitive testing across domains should be incorporated into future trials.[59]

KEY POINTS

- **Prognosis of CNS lymphoma has improved over the last few decades with widespread adoption of methotrexate-based therapy.**
- **Cognitive deficits and issues affecting quality of life are of increasing importance as survival in CNS lymphoma improves.**

CONCLUSION

CNS lymphoma presents unique challenges and opportunities to the neuro-oncologist. Although generally aggressive, it tends to be highly responsive to treatment, and the goal of therapy may be curative.

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Brain Metastases and Leptomeningeal Disease

By Priya Kumthekar, MD; Emilie Le Rhun, MD

REVIEW ARTICLE

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RELATIONSHIP DISCLOSURE:
Dr Kumthekar has received personal compensation in the range of $500 to $4999 for serving as a consultant for F. Hoffmann-La Roche Ltd., Janssen, and Orbus Therapeutics, in the range of $5000 to $9999 for serving as a consultant for Affinia Therapeutics, Clario, BPGbio, Inc., and Les Laboratoires Servier and on a speakers bureau for Seagen, Inc., and in the range of $10,000 to $49,999 for serving as a consultant for Biocept, Inc., Clario, EnClear Therapies, Inc., and Novocure GmbH. Dr Le Rhun has received personal compensation in the range of $500 to $4999 for serving as a consultant for Les Laboratoires Servier and Pierre Fabre and on a scientific advisory or data safety monitoring board for
Continued on page 1751

UNLABELED USE OF PRODUCTS/ INVESTIGATIONAL USE DISCLOSURE:
Dr Kumthekar and Dr Le Rhun discuss the unlabeled/ investigational use of ANG1005, cytarabine, ipilimumab, methotrexate, nivolumab, pemetrexed, pertuzumab, thiotepa, topotecan, and trastuzumab for the treatment of brain metastases and leptomeningeal disease.

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ABSTRACT

OBJECTIVE: **Central nervous system (CNS) metastases include brain parenchymal, spinal cord, and leptomeningeal metastases. This article discusses the diagnostic and therapeutic advances of the last decade that have improved outcomes for patients with these CNS metastases.**

LATEST DEVELOPMENTS: **The diagnostic tools for CNS metastases, particularly leptomeningeal disease, have evolved over the past decade with respect to advancements in CSF analysis. Multiple medical therapies are now available for brain metastasis treatment that have shown CNS efficacy, including targeted therapies and antibody-drug conjugates. Molecular testing for CNS metastases has become more common and the repertoire of molecularly targeted therapies continues to expand. Advancements in radiation therapy, including improvements in stereotactic radiation techniques, whole-brain radiation with hippocampal avoidance, and proton beam radiation, have changed the radiation management of patients with CNS metastases. New intrathecal agents are currently being tested for the management of leptomeningeal metastases.**

ESSENTIAL POINTS: **CNS metastases are far more common than primary brain tumors and are increasing in prevalence in the setting of improved treatments and prolonged survival in patients with systemic cancers. There have been many changes in the diagnostics and treatment of CNS metastases, yielding subsequent improvements in patient outcomes with further advancements on the horizon.**

INTRODUCTION

Central nervous system (CNS) metastases include both parenchymal brain metastases and leptomeningeal disease. With improvements in the survival of patients with systemic cancers and the development of screening brain MRI in the metastatic setting, the incidence of CNS metastases, specifically intracranial metastases which include brain metastases and leptomeningeal disease, has increased. Approximately 2% to 12% of patients with brain metastases may also have leptomeningeal disease at presentation, and up to 37% of patients with brain metastases may develop leptomeningeal disease during their clinical course.[1] Brain metastases are approximately 10 times more common than primary malignant brain tumors.[2] Malignancies with a high potential for intracranial metastasis (both parenchymal and leptomeningeal) include lung cancer (small

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cell and non–small cell), breast cancer, and melanoma.[2] Although these are the primary tumor types that have the greatest propensity to metastasize to the CNS, any primary cancer can result in CNS metastasis.

The terms *intracranial metastases* and *CNS metastases* are often used interchangeably, although at times erroneously. It is important to point out that intracranial metastases have different anatomic geographies (FIGURE 5-1). The term *brain metastases* should be used to describe brain parenchymal metastases only. Pachymeningeal metastases refers to cancer within the dura and arachnoid, whereas leptomeningeal disease includes disease of the arachnoid and pia (ie, the subarachnoid space and CSF). This article focuses on CNS-specific locations of the brain parenchymal and leptomeningeal spread of solid tumor malignancies and discusses the epidemiology, diagnosis, and treatment approach in CNS metastases.

Historically, patients with CNS metastases were frequently excluded from clinical trials. In July 2020, the US Food and Drug Administration (FDA) released guidance for industry on the inclusion of patients with brain metastases in clinical trials.[3] Prior to this guidance, the organization Friends of Cancer Research within the American Society of Clinical Oncology released their recommendations to include patients with CNS metastases in clinical trials.[4] Efforts to include patients with CNS metastases are ongoing with the hope that their inclusion in trials will more accurately reflect the true population regularly seen in the clinical setting.

EPIDEMIOLOGY

Melanoma, lung cancer, and breast cancer make up the majority of cases of intracranial metastasis.[5] Patients with breast cancer as a whole make up approximately 36% of patients with solid tumor brain metastases, the majority of these patients have triple-negative breast cancer (ie, negative for estrogen receptors, progesterone receptors, and *HER2* amplification) and *HER2*-positive breast cancer; combined, these patients make up roughly two-thirds of patients with breast cancer who have intracranial metastases. Outside of these more common primary cancers, renal cancer also has a high incidence of brain metastases, making up approximately 10% of patients with solid tumor brain metastases.[5]

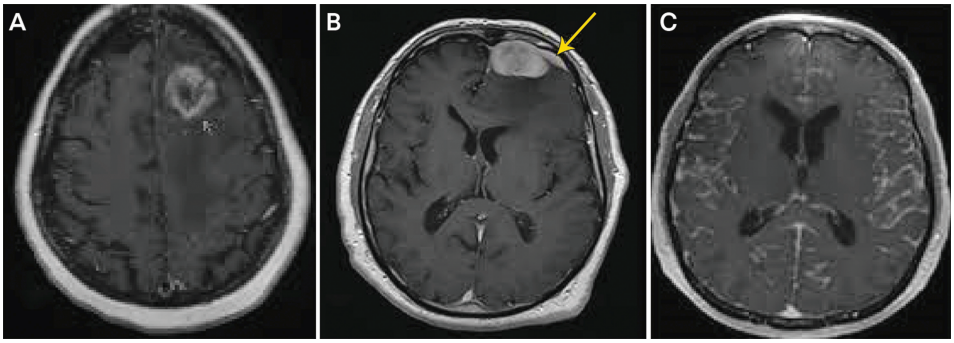

FIGURE 5-1
Axial T1-weighted postcontrast MRIs showing a brain parenchymal metastasis (*A*), dural-based metastasis (*B*, *arrow*), and leptomeningeal disease (*C*).

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Contributing to the increasing incidence of CNS metastasis, many of the novel therapeutics that improve outcomes for systemic cancers do not cross the blood-brain barrier or blood-CSF barrier, leading to the CNS being a sanctuary site for metastases. Additionally, as MRI brain scans become more readily accessible, systematic screening should be considered in the population of patients at risk; however, screening parameters are unclear and not uniform. Per the current National Comprehensive Cancer Center guidelines, screening at the time of diagnosis is only recommended for patients with select malignancies or those at certain stages of disease, including small cell lung cancer, non–small cell lung cancer, melanoma, testicular cancer, alveolar soft part sarcoma, angiosarcoma, and left-sided cardiac sarcoma. Despite a higher rate of CNS metastases, cancer subtypes such as triple-negative breast cancer or *HER2*-positive breast cancer lack screening parameters. The European Association of Neuro-oncology (EANO) and European Society for Medical Oncology (ESMO) guidelines identify entities that should benefit from a screening program, including stage IV melanoma, stage II/III/IV non–small cell lung cancer, and stage IV *HER2*-positive and triple-negative breast cancer.[6,7]

BRAIN METASTASES

Brain metastases can present with focal or generalized neurologic symptoms. Brain MRI with and without gadolinium contrast is the test of choice for the diagnosis of brain metastases and CSF cytology is the current best practice for identifying leptomeningeal disease.

Diagnosis

The clinical presentations of brain metastases can vary based on size, location, and degree of symptomatic cerebral edema. Neurologic presentations of brain metastases can be divided into two categories: generalized neurologic symptoms and focal neurologic symptoms. Generalized neurologic symptoms are typically a result of increased intracranial pressure and include headaches, nausea, vomiting, and lethargy. Focal neurologic symptoms include those related to tumor location and manifest in symptoms or signs such as motor and sensory deficits, speech abnormalities, frontal symptoms (eg, disinhibition, decreased attention, loss of executive function), memory impairment, and cognitive decline. Seizures may be observed in patients with brain metastases and typically manifest as focal seizures with secondary generalization. Asymptomatic presentations of brain metastases are also encountered, particularly in the setting of neuroimaging being performed for screening purposes, incidentally, or for clinical trial enrollment purposes.

The optimal imaging modality for detecting brain metastases is MRI with and without contrast (gadolinium). Brain metastases classically appear on T1 postcontrast sequences as contrast-enhancing masses since they disrupt the blood-brain barrier. Brain metastases are often associated with cerebral edema which on imaging appears as perilesional T2 or fluid-attenuated inversion recovery (FLAIR) hyperintensity, and this edema is often out of proportion to the lesion size. The presence of calcification, hemorrhage, and cystic components impacts the appearance of metastasis on many common MRI sequences. Brain metastases most commonly associated with hemorrhage include melanoma, renal cell carcinoma, thyroid carcinoma, and choriocarcinoma.[8]

KEY POINTS

- With improvements in systemic cancer therapies, patients are living longer and the prevalence of brain metastases is rising.
- Central nervous system (CNS) metastases from systemic cancers are more common than primary brain tumors and may occur within the brain and spinal cord parenchyma, leptomeninges, or the dura.
- The anatomic difference between dural, brain parenchymal, and leptomeningeal metastases should be distinguished since this impacts treatment decision making.
- The optimal imaging modality for brain metastasis imaging is brain MRI with and without contrast.
- Brain metastases most commonly associated with hemorrhage include melanoma, renal cell and thyroid carcinomas, and choriocarcinoma.

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MRI demonstrates better soft-tissue anatomical detail than CT; however, for some patients who cannot have MRI due to implanted devices or other MR-unsafe or MR-conditional factors, CT with and without contrast can also be performed. The overall sensitivity of CT for brain metastases is low, particularly with noncontrast CT in which case sometimes the only evidence of brain metastases is hypodensities corresponding to cerebral edema. Contrast-enhanced CT improves this sensitivity but does not match that of MRI.[9] Additionally, CT scanning exposes the patient to further ionizing radiation, but is the preferred imaging method when evaluating for bony lesions such as calvarial lesions.

MRI techniques can be used to acquire a wealth of information on metastases or other intracranial pathologies that go beyond anatomy to include both metabolic and physiologic information through diffusion, perfusion, spectroscopy, and other advanced imaging techniques. Positron emission tomography (PET) scanning has also advanced with the more widespread adoption of amino acid tracers replacing traditional fludeoxyglucose, with improvements in signal-to-noise ratio and diagnostic specificity.[9] These advanced imaging techniques can potentially help distinguish tumor progression from treatment-related effects caused by radiation or immunotherapy. Although out of the scope of this article, it is important to also consider possible differential diagnoses, including primary brain tumors, abscesses, or inflammatory lesions, even in the presence of a histologically confirmed cancer. A confirmed diagnosis of brain metastases can technically only be obtained by histology of a tumoral sample obtained with biopsy or resection.

Therapeutic Approaches

Treatment for intracranial metastases calls for a multimodality and multidisciplinary approach that can involve surgery, radiation, and medical therapy. The approach to treatment is twofold: 1) prolong survival in the setting of typically noncurable disease and 2) preserve quality of life by preventing new neurologic deficits or delaying further neurologic deterioration. Tumor-directed treatment is typically achieved through three primary modalities: surgery, radiation, and medical therapy.

SURGERY FOR BRAIN METASTASES. Surgery can be utilized in the setting of brain metastases as a diagnostic or therapeutic tool. While the lesion pattern on a brain MRI could guide the diagnosis of brain metastases without surgical intervention, surgery may be required in the presence of diagnostic uncertainty, such as when a primary tumor is unknown, when distinguishing brain metastases from radiation necrosis, or when the patient has a cancer known to only rarely generate brain metastases. Only a histologic analysis of a surgically sampled tissue can confirm the diagnosis of brain metastases with 100% certainty. Brain metastases may also display "branched evolution" whereby there may be genomic alterations of the tumor or microenvironment that may differ in comparison to the primary cancer site.[10] For this reason, an update of the molecular profiling may be recommended at the time of diagnosis of a new metastatic lesion if the lesion is surgically low risk. When surgery is planned, it is important to reassess the tissue for the molecular profile of the tumor, particularly to ascertain if there are specific potential targeted therapies available.

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SURGERY AS A THERAPEUTIC TOOL. Resection of single brain metastases in patients with controlled systemic cancer has been demonstrated to improve clinical outcomes. The extent of resection has been shown to be associated with local control (ie, the local recurrence of disease).[11,12] An en bloc resection is recommended to reduce the risk of leptomeningeal dissemination. A brain MRI should be performed within 48 hours after surgery to assess the extent of resection.[7]

Other indications for surgery include large brain metastases associated with increased intracranial pressure or neurologic deficits even in patients with multiple brain metastases. Brain metastases located in the posterior fossa should be discussed with the neurosurgical team in an expedited manner due to the risk of obstructive hydrocephalus. Neurosurgery should also be considered for patients with symptomatic cystic lesions or possible symptomatic radionecrosis. Finally, surgery should be considered to allow steroid dose reduction, particularly when immunotherapy represents a therapeutic option in a steroid-dependent patient who may have compromised immunotherapy efficacy in the setting of concurrent steroid administration.[13]

Laser interstitial thermal therapy is a new approach that may be utilized in the setting of brain metastases. Laser interstitial thermal therapy is a minimally invasive surgery that involves inserting a laser catheter into a specific lesion and heating it to temperatures that are high enough to kill the metastatic tumor. When laser interstitial thermal therapy is used, a biopsy is performed prior to heating the lesion. Early data have been encouraging for the treatment of brain metastases or radionecrosis in small cohorts[14]; however, randomized trials have not yet been published.

RADIOTHERAPY FOR BRAIN METASTASES. For decades, radiation therapy has been the backbone of brain metastasis treatment and has included both whole-brain radiation therapy and more focal stereotactic radiosurgery. More recently, stereotactic radiosurgery has become the mainstay for the treatment of brain metastases and the surgical cavity after brain metastasis resection. Stereotactic radiosurgery allows for the delivery of higher doses of radiation with 1-mm precision. It can be given in one dose or multiple fractions, the latter being preferred for larger lesions, lesions adjacent to eloquent cortex, or previously irradiated areas. Stereotactic radiosurgery was commonly used for the treatment of one to three brain metastases,[15] but a contemporary randomized trial showed similar survival in patients with five to ten lesions compared with patients with one to four lesions,[16] and stereotactic radiosurgery is now commonly used for more than four lesions.

Whole-brain radiotherapy after surgical resection or stereotactic radiosurgery has been shown to improve local and distant brain metastasis control in randomized trials, but not necessarily overall survival, and patients had more adverse events in the whole-brain radiotherapy group.[17] Another randomized trial compared postoperative stereotactic surgery with observation and showed better local control after postoperative stereotactic radiosurgery.[18] In a randomized trial involving brain metastases of melanoma previously operated on or treated by radiosurgery, the distant intracranial failure rates within 12 months with or without whole-brain radiotherapy were similar. The survival rate and proportion of patients who did not experience a decrease in performance status were also similar between the two arms.[19] In the Quality of Life after Treatment

KEY POINTS

- The management of brain metastases may include a combination of surgery, radiation, or medical therapy, and ideally treatment decision making should involve a multidisciplinary clinical team of physicians.
- Surgery may be indicated for brain metastases, particularly for solitary or symptomatic tumors.
- When brain metastasis tissue is available, molecular testing should be considered since its molecular profile could vary from the primary cancer site.
- Stereotactic radiosurgery has become the mainstay for the treatment of brain metastases and is typically preferred over whole-brain radiation therapy when possible.
- Whole-brain radiotherapy with hippocampal avoidance has been shown to be less detrimental to patients' cognition in comparison to traditional whole-brain radiotherapy.
- Novel molecularly targeted agents and antibody-drug conjugates that cross the blood-brain barrier are available for CNS metastases, particularly for *HER2*-positive and harbor epidermal growth factor receptor genetic variations.

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for Brain Metastases (QUARTZ) trial, patients with brain metastases from non–small cell lung cancer who were not eligible for surgery or stereotactic radiosurgery were randomized between whole-brain radiotherapy and supportive care. The median survival rates were similar between the two arms, and the quality of life was not reduced in the group receiving palliative care only.[20] Another important consideration is that whole-brain radiotherapy increases the risk of neurocognitive decline.[17,19,21] Some teams recommend neuroprotective treatment with oral memantine 10 mg twice daily based on the results of a trial by the Radiation Therapy Oncology Group.[22] A randomized phase 3 trial compared whole-brain radiation therapy plus memantine with and without hippocampal avoidance and showed potential preservation of cognition with the addition of hippocampal avoidance.[23] Whether the effect was related to hippocampal avoidance only or a synergistic effect between hippocampal avoidance and memantine remains unclear.

Several trials are currently exploring the role of stereotactic surgery before the surgical resection of a brain metastasis, with the goal of reducing the risk of meningeal dissemination. The best dosing and timing regimen and the value of this approach remain to be demonstrated.

SYSTEMIC PHARMACOTHERAPY. The role of systemic pharmacotherapy for the treatment of brain metastases has grown in recent years. Very little data from phase 0 trials are available to provide insight into the intrabrain metastases penetration of the drugs and their activity in the brain parenchyma. After a brain metastasis surgery, the updated molecular data should supercede the original molecular data of the primary or a metastatic tumor. **FIGURE 5-2** depicts key molecular targets found in brain metastases with respective available systemic treatment agents. It is also important to be aware of potential drug-drug interactions with other systemic treatments. Specifically, special attention should be paid to the use of dexamethasone for cerebral edema as data suggest steroids negatively impact the efficacy of immunotherapy.

BRAIN METASTASES FROM MELANOMA. The preferred first-line option for asymptomatic or paucisymptomatic patients not requiring steroids is a combination of nivolumab and ipilimumab,[24,25] including in patients with a *BRAF* gene variation. Both of these agents are immune checkpoint inhibitors with differing mechanisms of action with nivolumab targeting programmed cell death protein 1 and ipilimumab targeting cytotoxic T lymphocyte associated protein 4. The phase II CheckMate 204 study included asymptomatic patients with brain metastases, and 5-year follow-up data showed an intracranial response rate of 55% and the 36-month overall survival rate had not yet been reached for 72% of patients, which demonstrates both the efficacy and durability of this response. It is important to note that neurologically symptomatic patients and those already on steroids did not appear to benefit from this treatment.[26]

Up to 50% of patients with melanoma who have CNS metastases may harbor a *BRAF* variation, the most common of which is the $BRAF^{V600E}$ variation. *BRAF* inhibition monotherapy with dabrafenib was studied in the BREAK-MB trial and showed an intracranial response rate of 39%.[27] Adding MEK inhibition to *BRAF* inhibition helps to overcome drug resistance, which led to the COMBI-MB trial that studied the combination of dabrafenib and trametinib in patients with $BRAF^{V600}$-variant brain metastases. Intracranial responses as high as 58% were

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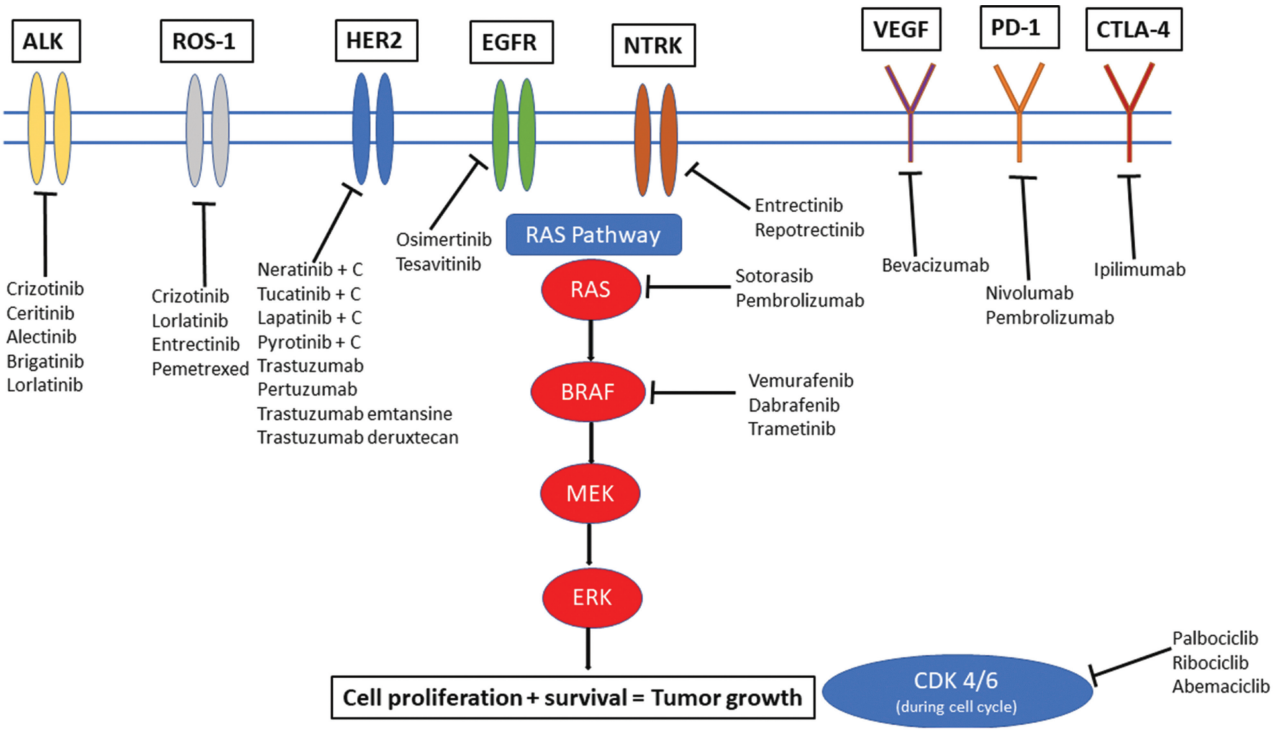

FIGURE 5-2

Systemic therapies with central nervous system activity illustrated by molecular targets.

C = capecitabine.

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seen in these patients, which included cohorts of previously treated (with radiation therapy) and untreated patients. However, the duration of response is limited to 6 to 7 months with the combination of vemurafenib and dabrafenib.[27-30] Conventional chemotherapy such as temozolomide has shown limited efficacy.

BRAIN METASTASES FROM LUNG CANCER. Lung cancer has undergone an evolution in categorization over the past decade as patients may have potentially targetable genetic variations, including epidermal growth factor receptor (*EGFR*), ALK receptor tyrosine kinase (*ALK*), ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*), and KRAS proto-oncogene, GTPase (*KRAS*) variations, ret proto-oncogene (*RET*) rearrangements, fibroblast growth factor receptor alterations, and even *HER2* variations. These mutations are typically seen in non–small cell lung cancer as opposed to small cell lung cancer, and therefore these targeted therapeutics are more prevalent in the non–small cell lung cancer setting.

In patients without one of these actionable oncogenic driver alterations, immune checkpoint inhibitors either as monotherapy or in combination with platinum-based chemotherapy are typically the preferred option. However, there are limited data on patients with newly diagnosed or progressing brain metastases. Data from a phase 2 trial showed a 30% response rate in patients with previously untreated brain metastases who were treated with pembrolizumab, another immune checkpoint inhibitor that targets

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programmed cell death protein 1.[31] When combined with conventional chemotherapy, pembrolizumab showed more benefit with a response rate of 39% (versus 19.7% for chemotherapy alone) and a durable response with a median overall survival time of 18 months versus 7.6 months.[32] The efficacy of nivolumab was studied in a retrospective cohort of patients with asymptomatic brain metastases, with an intracranial control rate of 44% among patients with progressing or newly diagnosed brain metastases.[33] Unfortunately, most immunotherapy trials have only enrolled patients with controlled and pretreated brain metastases.

CNS responses have also been observed with targeted therapies in non–small cell lung cancer with oncogenic driver variations, such as *EGFR*, *ALK*, *ROS1*, and *KRAS* variations, *RET* rearrangements, and fibroblast growth factor receptor alterations.

In a phase 2 trial using the third-generation tyrosine kinase inhibitor simertinib, a response rate of 40.5% and improved median progression-free survival were noted in patients with non–small cell lung cancer and *EGFR* variations presenting with radiotherapy-naive brain metastases.[34] When compared with prior-generation tyrosine kinase inhibitors, simertinib demonstrated a CNS objective response rate of 91% and a median progression-free survival rate that was not reached versus 13.9 months in the control arm.[35] Newer-generation ALK inhibitors such as alectinib and brigatinib have shown similar success with intracranial response rates of up to 78%.[36,37] Additional clinical trials targeting ALK, KRAS, neurotrophic receptor tyrosine kinase, and others in lung cancer CNS metastases are ongoing.

BRAIN METASTASES FROM BREAST CANCER. As previously mentioned, the majority of breast cancer intracranial metastases come from triple-negative and *HER2*-positive cancers. *HER2*-directed therapy has historically had minimal blood-brain barrier penetration, but this has fortunately changed with newer-generation *HER2*-directed agents. Agnostic to breast cancer subtype, standard chemotherapy such as capecitabine, cisplatin, etoposide, vinorelbine, and gemcitabine may demonstrate response rates of around 30% to 40%.[38]

In patients with *HER2*-positive breast cancer, anti-*HER2* agents are preferred. Similar to systemic agents in melanoma and lung cancer, most of these treatments were evaluated in randomized trials not dedicated to brain metastases. Additionally, most patients with brain metastases enrolled in these trials were patients with stable brain metastases (ie, lesions not needing immediate treatment) following local treatment (non-treatment-naive). The phase 3 randomized HER2CLIMB trial compared tucatinib, capecitabine, and trastuzumab, which binds to HER2, with capecitabine and trastuzumab in patients with metastatic *HER2*-positive breast cancer. In a subanalysis of the 291 patients with brain metastases (87 classified as having active brain metastases at enrollment), a prolonged survival time was noted in the tucatinib combination group compared with the trastuzumab and capecitabine group (18.1 versus 12.0 months in the whole population of patients with brain metastases and 20.7 months versus 11.6 months in the population with active brain metastases).[39] The TUDEXO-1 trial was a single-arm trial involving patients previously treated with trastuzumab and pertuzumab, another HER2-binding therapy, with newly diagnosed brain metastases or brain metastases

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progressing after previous local therapy and no indication for immediate local therapy. Fifteen patients were enrolled and received trastuzumab deruxtecan, a HER2 antibody-drug conjugate. Eleven of the 15 enrolled patients had an intracranial response.[40] Together, these studies paved the way for the use of tucatinib and trastuzumab deruxtecan in the setting of *HER2*-positive brain metastases.

INTEGRATED APPROACHES. Therapeutic recommendations in the setting of CNS metastases should ideally be made by a tumor board in the presence of an experienced multidisciplinary physician team including representation from neurology, neuroradiology, neurosurgery, neuropathology, medical oncology, and radiation oncology. The role of systemic pharmacotherapy is increasing, particularly in patients with asymptomatic or paucisymptomatic brain metastases, and the timing of these therapies with respect to stereotactic radiosurgery and surgery remains to be clearly established (**CASE 5-1**). No standardized options or clear treatment algorithms are defined at recurrence. Guidance is provided by the National Comprehensive Cancer Center and the EANO-ESMO guidelines.[7,41] The best potential medical approach for first-line treatment and treatment at recurrence should also consider each patient's functional and neurologic status, the histologic and molecular subtype of cancer, medical history, prior treatments received, and potential adverse events of therapeutic approaches. Patient follow-up should ideally use clinical assessment and concurrent imaging with MRI or PET.

SYMPTOMATIC CARE. Steroids, namely dexamethasone, can be utilized to decrease cerebral edema when patients are symptomatic. Ideally, steroids should be used in a limited fashion until more definitive tumor-directed treatment can be implemented. Steroid dosing should be titrated to each patient's symptomatic need and not to the degree of edema seen on neuroimaging. If patients are asymptomatic or paucisymptomatic, steroids should not be given merely for edema seen on neuroimaging. Primary seizure prophylaxis is not recommended for patients with intracranial metastases.[42]

When antiseizure drugs are indicated, potential interactions with anticancer therapy should be considered. Drugs such as levetiracetam, lamotrigine, and lacosamide are preferred given their limited drug-drug interactions. Treatment for venous thromboembolism is not contraindicated in patients with intracranial metastases as long as there is no active intracranial hemorrhage. Primary thromboprophylaxis can also be considered for inpatients with acute illness or who are confined to bed.

Radiation necrosis involves inflammatory injury to the brain and can occur after radiation, particularly with repeated radiation therapy or in combination with certain systemic therapies. The first-line therapy in symptomatic patients is typically a short course of glucocorticoids; however, if a prolonged course is required other interventions may be necessary. Neurosurgical intervention with either resection or laser interstitial thermal therapy can be used, and medical therapy with bevacizumab can also be considered.

PATIENT AND IMAGING FOLLOW-UP. A clinical and imaging follow-up with brain MRI should be performed at least every 3 months or whenever clinically indicated. Standardized neurologic scorecards such as the one proposed by the

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CASE 5-1

A 44-year-old woman presented with a right breast lump and was found to have T2N1 estrogen receptor–positive breast cancer (progesterone receptor–negative, *HER2*-negative). She underwent bilateral mastectomy (and later bilateral oophorectomy) followed by chemotherapy with doxorubicin, cyclophosphamide, and paclitaxel therapy. She then began tamoxifen therapy which she continued for 10 years without cancer recurrence.

Twelve years after her initial diagnosis, she presented with back pain and was found to have vertebral (bony) metastases. Emergent workup revealed bony metastases with cord compression at T12 (FIGURE 5-3). She underwent emergent T10 to L1 laminectomy and T9 to L2 segmental instrumentation followed by adjuvant spine radiation. Brain imaging showed no evidence of brain metastases. She was started on fulvestrant and palbociclib. Later that year, systemic progression was noted and she was started on capecitabine. Brain MRI was performed to restage and an anterior left temporal dural-based metastasis was found (FIGURE 5-4). Given the possibility of a leptomeningeal component, leptomeningeal workup was conducted, including spine MRI which showed no radiographic evidence of leptomeningeal disease, and CSF cytology which was negative. Months after starting on capecitabine, she was noted to have progression of this dural-based lesion as well as on systemic imaging and was changed to trastuzumab deruxtecan in the setting of *HER2* low disease (immunohistochemistry 1+). She also underwent stereotactic radiosurgery to the left middle cranial fossa temporal lobe lesion. Afterward, she was followed with both central nervous system (CNS) and systemic imaging and remained stable on trastuzumab deruxtecan.

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FIGURE 5-3
Sagittal T2-weighted spine MRI of the patient in CASE 5-1 showing a bony metastasis at T12 with subsequent compression of the spinal cord.

FIGURE 5-4
Axial T1-weighted brain MRI of the patient in CASE 5-1 following administration of gadolinium contrast showing a homogenously enhancing lesion at the left anterior temporal pole consistent with dural-based metastasis.

COMMENT

This case illustrates multiple points. The first is that spinal cord compression is a neurologic emergency. This patient was able to undergo emergency surgery to relieve this compression, followed by radiation. Additionally, if there is a concern for leptomeningeal disease, a workup including clinical evaluation, whole neuraxis brain MRI imaging, and CSF cytology analysis is warranted. The case further illustrates the expanding armamentarium of targeted therapies available for CNS metastases. Given that this patient's disease was shown to be "*HER2* low" she was able to be treated with trastuzumab deruxtecan, which has been shown to have CNS efficacy. Of note, the effect of trastuzumab deruxtecan on the CNS irradiated lesion cannot be assessed.

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KEY POINTS

- Spinal cord compression can be a complication of CNS or vertebral metastases and is considered a neurologic emergency.
- The diagnosis of leptomeningeal disease is definitively confirmed by positive CSF cytology for malignant cells, although the sensitivity of this test is only about 50% to 70% for the initial CSF sampling.
- Novel diagnostics including CSF circulating tumor cells and tumoral DNA are being investigated as next-generation diagnostic tools for leptomeningeal disease.

Response Assessment in Neuro-oncology group may be used.[43] Imaging protocols should be consistent over time[44] and standard criteria should be used.[45,46] Amino acid PET tracers such as [^{11}C]-methyl-L-methionine, 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine, and O-(2-[^{18}F]fluoroethyl)-L-tyrosine are emerging modalities that may help distinguish progression or radionecrosis after treatment with radiation; however, further prospective validation is ongoing.[47]

LEPTOMENINGEAL DISEASE

The diagnosis of leptomeningeal disease includes three key components: clinical findings, neuroimaging, and abnormal CSF cytology. Clinical efforts should include assessing for cranial nerve and spinal nerve root deficits. Neuroimaging can show typical leptomeningeal disease contrast enhancement at the cerebral and spinal levels and CSF cytology can show positive signs of malignancy.

Standard Workup for Leptomeningeal Metastases

Clinical neurologic manifestations of leptomeningeal disease include the involvement of cranial and spinal nerves that wind through the subarachnoid space, and therefore symptomatology may include cranial nerve deficits and spinal nerve dysfunction. Cranial nerve dysfunction can be indicated, for example, by diplopia, dysarthria, dysphagia, facial weakness, or sensory disturbance, including the so-called numb chin syndrome classically associated with leptomeningeal disease. Spinal nerve dysfunction can be indicated by polyradiculopathy or bowel and bladder dysfunction as well as saddle anesthesia. Early bowel dysfunction is often described by patients as constipation and bladder dysfunction often presents as loss of sensation to urinate.

Patients with symptoms suggestive of leptomeningeal disease or with radiographic findings compatible with leptomeningeal disease should undergo a complete MRI of the entire neuraxis (FIGURE 5-5).[48] The characteristic imaging abnormalities on brain MRI are diffuse leptomeningeal enhancement following the sulci and gyri on postcontrast sequences, including at the cortical surfaces, basal cisterns, cerebellar folia, and cranial nerves.[49] FLAIR hyperintensity, particularly in the sulci, may be seen as a consequence of elevated protein.[50] The typical MRI spine findings of leptomeningeal disease include enhancement of the nerve roots, including at the cauda equina, or clumping of the nerve roots within the cauda equina.

The diagnosis of leptomeningeal disease is definitively confirmed by positive CSF cytology for malignant cells, although the sensitivity of this test is only about 50% to 70% for the initial CSF sampling.[51] With repeated samplings, persistently negative cytology results may be seen in up to 20% of patients with leptomeningeal disease, perhaps reflecting meningeal adherence rather than entrance into the CSF space itself.[52] A minimum of 5 ml of CSF, ideally without blood contamination, should be collected for the cytological analysis. CSF analysis may also show elevated protein, lymphocytic pleocytosis, and low glucose, although approximately 5% of patients with leptomeningeal disease display normal CSF findings.[53] Given these limitations, advanced modalities to assess CSF are under investigation (discussed in the next section of this article).

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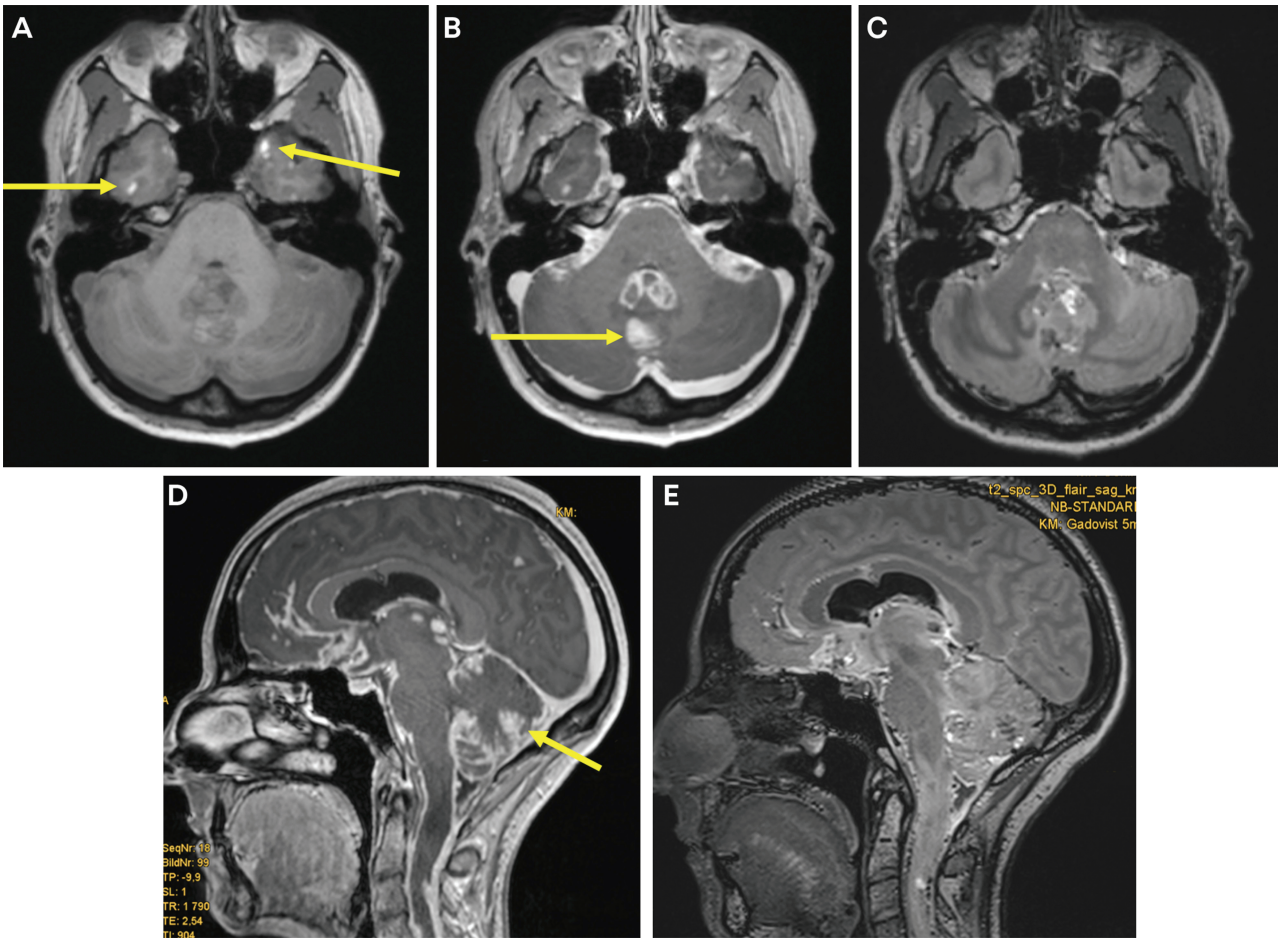

FIGURE 5-5

Typical MRI findings of leptomeningeal disease from melanoma. *A*, Axial T1-weighted brain MRI without contrast showing small hemorrhagic lesions (*arrows*) in the context of central nervous system metastases of a melanoma. *B*, Axial T1-weighted brain MRI following administration of gadolinium contrast showing metastases (*arrow*). *C*, Axial fluid-attenuated inversion recovery (FLAIR) brain MRI following administration of gadolinium contrast, *D*, Sagittal T1-weighted brain MRI following administration of gadolinium contrast showing typical linear contrast enhancement suggestive of leptomeningeal metastases on the cranial nerves and periphery of the brainstem, and ventricular cistern, as well as a cerebellar meningeal nodule (*arrow*). The leptomeningeal metastases are not associated with edema. *E*, Sagittal FLAIR brain MRI following administration of gadolinium contrast.

Tools Under Development for the Diagnosis of Leptomeningeal Metastases

In the setting of the diagnostic limitations for patients with suspected leptomeningeal disease, a variety of noncytology CSF-based diagnostic assays are under development including cancer-specific biomarkers, tumor-specific RNA, circulating tumor cells, and circulating tumor DNA. Of note, their role in clinical practice has not been clearly established to date.

CIRCULATING TUMOR CELL DETECTION IN CSF. Circulating tumor cells are tumor cells that have essentially been sloughed off from the primary tumor and appear within a bodily fluid, classically the bloodstream. One commercial assay has been FDA approved for the detection of circulating tumor cells

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expressing epithelial cell adhesion molecule, a transmembrane glycoprotein in the blood.[54,55] Circulating tumor cell technology is being tested more often in the setting of CNS malignancies and metastases, including brain parenchymal metastases and leptomeningeal disease. A 2020 prospective study tested an epithelial cell adhesion molecule immunoflow cytometry assay for circulating tumor cell detection in 81 patients with suspected and confirmed leptomeningeal disease.[56] The sensitivity of the circulating tumor cell assay was 94% compared with 76% for CSF cytology, and the specificity was 100%.

CIRCULATING TUMOR DNA DETECTION IN CSF. Cell-free DNA comprises DNA fragments that are approximately 100 to 200 nucleotides long and are released from dying cells as part of the cell turnover process, and represent a normal component of plasma. In cancer, a portion of circulating cell-free DNA arises from tumor cells and is termed circulating tumor DNA.[57] The identification of plasma circulating tumor DNA is associated with risk for metastases, recurrence, and poor prognosis in several cancer types.[58]

In the case of CNS metastases, plasma circulating tumor DNA appears to be less prevalent, challenging its utility for diagnosing leptomeningeal disease.[59] However, next-generation sequencing technologies may be applied to detect circulating tumor DNA in CSF.[59,60] Additionally, CSF circulating tumor DNA sequencing can identify actionable genetic alterations and molecular drivers, which may differ from those present in the primary tumor and plasma.[68] Despite these advancements, there remain some challenges and research is needed in the interpretation of CSF circulating tumor DNA to best understand technical factors such as background noise, bioinformatic thresholds, and the distinction between cell-free DNA and tumoral DNA.[61,62]

Classification of Leptomeningeal Metastases

A classification of leptomeningeal metastases has been proposed by the EANO-ESMO group to provide appropriate therapeutic options for patients with leptomeningeal metastases (FIGURE 5-6).[63] This classification is based on the results of clinical, imaging, and CSF cytology assessments, which are the three current pillars for the diagnosis of leptomeningeal metastases. The EANO-ESMO classification has been shown to have prognostic value in retrospective cohorts of patients.[64,65] It may also be used to guide therapeutic decisions.[64]

Therapeutic Approach to Leptomeningeal Disease Treatment

The median survival time is on the order of months for patients with leptomeningeal disease and the goal for most patients is to preserve quality of life by preventing new neurologic deficits or delaying further neurologic deterioration. Treatment for leptomeningeal disease largely involves radiation and medical management and, as opposed to parenchymal brain metastases, does not involve surgery as a mainstay.

Pharmacotherapy for Leptomeningeal Metastases

Medical therapy for leptomeningeal disease is limited and can be categorized into systemically administered agents and intrathecal agents. The latter are delivered directly into CSF and are indicated for a subset of patients with leptomeningeal disease.

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GENERAL PRINCIPLES OF SYSTEMIC PHARMACOTHERAPY IN LEPTOMENINGEAL DISEASE. Leptomeningeal metastases are often diagnosed in the context of already present metastatic disease, including brain metastases. These non–leptomeningeal disease metastases are often progressive at the time of the diagnosis of leptomeningeal metastases and also require treatment consideration. Systemic pharmacotherapy should always be considered among the therapeutic options for the treatment of leptomeningeal metastases.[63] It is commonly combined with other therapeutic approaches, such as intrathecal pharmacotherapy or radiotherapy. Systemic pharmacotherapy includes cytotoxic chemotherapy, targeted therapy, and immunotherapy. The choice of the systemic agent depends on tumor characteristics (eg, histology, molecular subtype), patient characteristics (eg, age, general and neurologic statuses, comorbidities), and previously administered treatments. As mentioned before, a drug's ability to reach the CSF compartment via the blood-CSF barrier should also be considered. No randomized trials of systemic therapy have been performed in patients with newly diagnosed leptomeningeal metastases. Only limited data from phase 2 trials are available. Most of the time, the choice of the best candidate drug has to be extrapolated from trials in patients with brain metastases or advanced metastatic disease. High-dose systemic cytotoxic therapies such as high-dose methotrexate[66] or pemetrexed[67] have shown modest success, but they need to be weighed against the risk of toxicity and the compatibility with other systemic drugs as well.

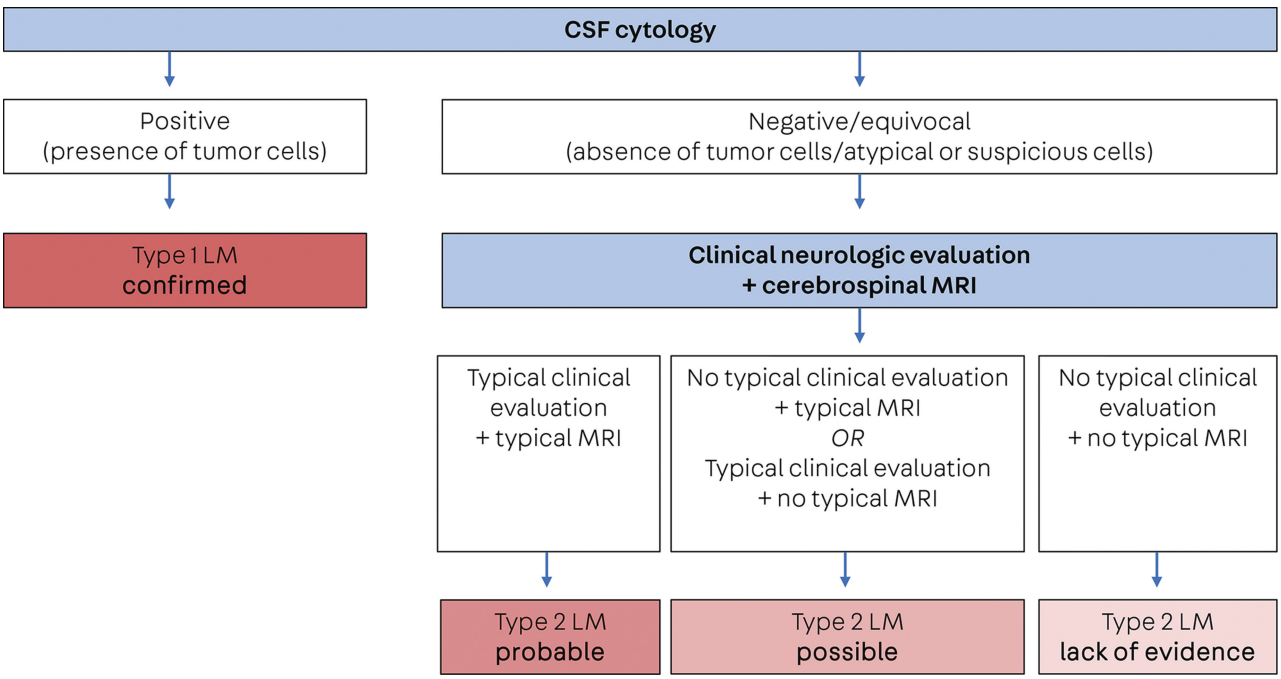

FIGURE 5-6

European Association of Neuro-oncology/European Society for Medical Oncology classification of leptomeningeal metastases.

CSF = cerebrospinal fluid; LM = leptomeningeal metastases; MRI = magnetic resonance imaging. Modified from Le Rhun E, et al. Ann Oncol.[70] © 2017 European Society for Medical Oncology. Published by Elsevier Ltd.

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In patients with non–small cell lung cancer with oncogenic driver variations such as *EGFR* and *ALK*, the preferred option is a targeted treatment. Promising results have been reported with osimertinib in patients with *EGFR* variations, with reported survival times of up to 13.3 months.[68] The best dose has not yet been established. Case reports and small cohorts have reported the use of systemic immunotherapy in patients with leptomeningeal metastases. Clinical trials are ongoing.

A response rate of 8% and a survival time of 8 months were observed in a phase 2 trial conducted with ANG1005, a taxane derivative, for patients with leptomeningeal metastases from breast cancer.[69] Pilot studies have also been

CASE 5-2

A 52-year-old man was diagnosed with an epidermal growth factor receptor (*EGFR*) Del 19 variation, TTF1-positive lung adenocarcinoma. Synchronous brain, bone, and liver metastases were found at the time of initial diagnosis. The patient was in good general health and was started on osimertinib 80 mg per day, a third-generation *EGFR* inhibitor. Local radiotherapy was also performed for four bone lesions and a liver metastasis. More than 20 supratentorial brain metastases were reported on the brain MRI (FIGURE 5-7A). A central nervous system (CNS) response was noted on the next MRI a month later (FIGURE 5-7B).

Both CNS and extra-CNS diseases were controlled and 11 months after his initial presentation his osimertinib dosage was reduced to 40 mg/day because of nail and cutaneous toxicity.

Eight months later the patient presented with headaches and radicular pain in the left arm.

Brain MRI showed new contrast-enhancing lesions suspicious for leptomeningeal metastases (FIGURE 5-7C) that were not observed on a routine brain MRI performed 4 weeks earlier (FIGURE 5-7D). The spinal MRI did not show any pathologic contrast enhancement. Tumor cells were observed in the CSF. The extra-CNS disease was stable. The osimertinib dosage was increased to 80 mg per day and control of the leptomeningeal metastases was maintained for 10 months, at which time the patient presented with both progression of leptomeningeal metastases and liver metastases. Whole-brain radiotherapy and liver metastasis stereotactic radiotherapy were performed, and he passed away 2.5 months after the end of whole-brain radiotherapy.

COMMENT

This case illustrates the improved efficacy with a rapid response to new systemic pharmacotherapy for CNS metastases, allowing for avoidance of whole-brain radiotherapy at the time of diagnosis of multiple brain metastases. This is also a typical example of new neurologic symptoms revealing leptomeningeal disease in a patient with controlled brain metastases at the routine follow-up performed 1 month earlier, demonstrating the importance of neurologic clinical assessment and the need for rapid updates to the CNS workup in the presence of changes in neurologic symptoms.

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performed with bevacizumab combined with etoposide and cisplatin (eight patients enrolled) or with abemaciclib in patients with hormone receptor–positive breast cancer (ten patients enrolled), with survival times of 4.7 months and 8.4 months, respectively.[70,71]

Targeted anti-*HER2* therapy with tucatinib (17 patients enrolled)[72] was assessed in prospective trials and promising results were reported, with survival times of up to 12 months. Immunotherapy with pembrolizumab was explored in 17 patients with breast cancer with leptomeningeal metastases, and median survival times of 3.4 months for *HER2*-negative patients and 5.1 months for all others were reported.[73]

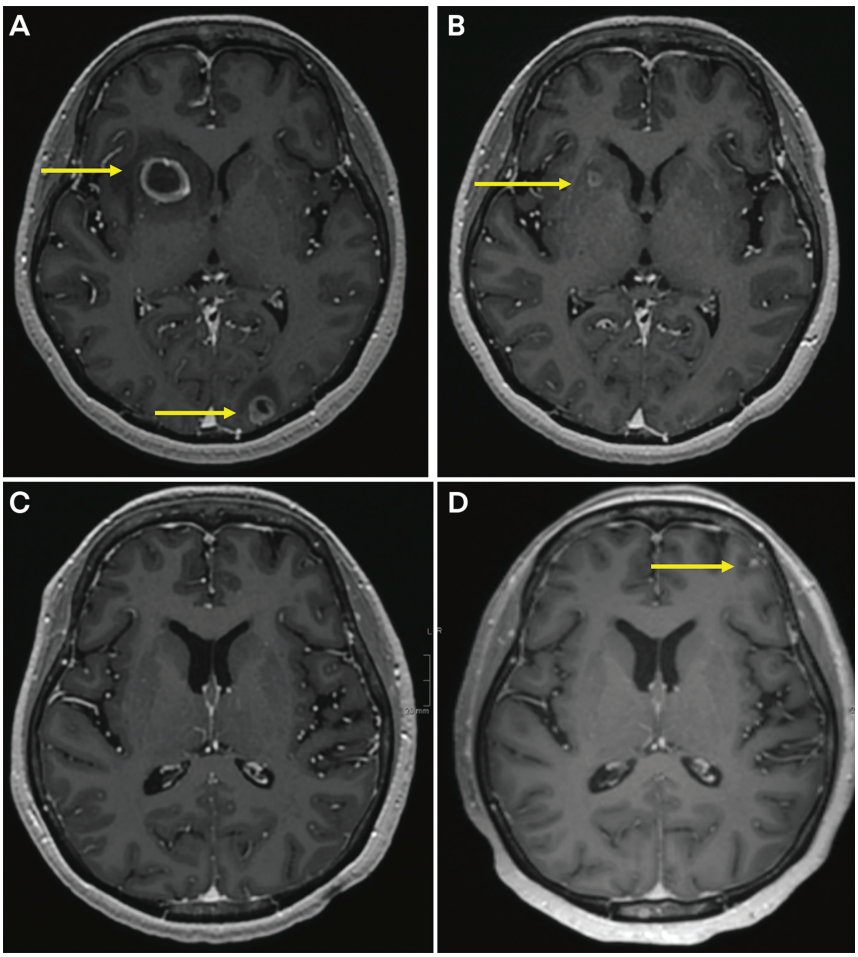

FIGURE 5-7

Axial T1-weighted brain MRI of the patient in CASE 5-2 following administration of gadolinium contrast. *A*, Two brain parenchymal metastases (*arrows*) identified at the time of the lung cancer diagnosis. *B*, One month after initiation of osimertinib 80 mg/day, demonstrating partial response (*arrow*). *C*, Routine surveillance image, 1 month before the diagnosis of leptomeningeal disease. *D*, A new contrast-enhancing leptomeningeal lesion (*arrow*) identified at the time of the leptomeningeal disease diagnosis.

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KEY POINT

- In specific clinical scenarios, intrathecal therapy can be considered for the treatment of leptomeningeal disease.

INTRATHECAL TREATMENT. The rationale for intrathecal therapy is to achieve therapeutic concentrations of drugs in CSF. Most systemically administered anticancer agents exhibit poor blood-CSF barrier penetration. To be a proper candidate for intrathecal drug delivery, patients must have nonobstructive CSF flow. Additionally, intrathecally administered agents do not penetrate the brain parenchyma beyond 1 mm to 2 mm and therefore currently intrathecal agents should not be considered in the treatment of brain metastases or bulky leptomeningeal disease.

Most systemic agents have a CSF-to-plasma concentration ratio of less than 5%, with a higher ratio indicating better CSF penetration. A CSF-to-plasma ratio of 0.24% has been reported for trastuzumab in the treatment of *HER2*-positive breast cancer, which increased to 1.32% after brain irradiation and 2.04% in patients treated by brain irradiation and with a diagnosis of leptomeningeal metastases.[74] Only a few agents have higher ratios, such as osimertinib which is used in non–small cell lung cancer with *EGFR* variations and has a CSF-to-plasma ratio between 9% and 13%.[75]

Most randomized trials of intrathecal treatment have compared different intrathecal treatments and thus did not assess the role of intrathecal therapy itself. The limitations of these trials have been analyzed by the Response Assessment in Neuro-oncology leptomeningeal metastasis group.[76]

However, the efficacy of intrathecal therapy has been shown in one randomized trial involving patients with breast cancer and newly diagnosed leptomeningeal metastases. In this trial, the primary endpoint, to improve leptomeningeal progression-free survival time, was met, and patients treated with intrathecal liposomal cytarabine had a significantly longer leptomeningeal progression-free survival time (4.2 months versus 2.2 months; hazard ratio = 0.61, $P = 0.04$). The overall survival time also tended to be longer in these patients (7.3 months versus 4.0 months; hazard ratio = 9.85, $P = 0.51$).[63] The probable benefit from intrathecal therapy has also been shown in a retrospective cohort of 254 patients, where patients with tumor cells in CSF had a significantly longer survival time compared with patients not treated with intrathecal therapy (3.8 months versus 1.8 months; $P = 0.018$).[64]

Different intrathecal drugs can be used, such as methotrexate, thiotepa, and cytarabine, all of which have specific regimens of administration (TABLE 5-1[70,77-83]). Folate administration is required for prophylaxis against systemic side effects caused by intrathecal methotrexate.[63] More recently, phase 1/2 data support the use of trastuzumab in patients with *HER2*-positive leptomeningeal disease; however, randomized trials are still needed to confirm the efficacy of this approach.[82-84] Other agents such as pemetrexed, pertuzumab, nivolumab, and ipilimumab are currently under investigation for intrathecal use. Although the safety of intrathecal trastuzumab and intrathecal nivolumab has been shown in phase 1/2 studies, the efficacy of this approach has not been demonstrated and the drugs are not approved for the treatment of leptomeningeal metastases. Intrathecal therapy can be administered via lumbar puncture or ventricular devices. Ventricular devices are usually the preferred option since this route ensures that the drug is delivered into the right compartment, is more comfortable for patients, and may improve patient outcomes, notably when short–half-life agents are used.[85] Complications with ventricular devices may be observed but the revision rate is very low. Intrathecal treatment must be performed by physicians trained in this procedure, under strictly aseptic conditions.

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Radiation Therapy for Leptomeningeal Metastases

Radiation therapy has historically been the mainstay of leptomeningeal disease treatment. However, there has been a trend toward delaying radiation therapy given the growing number of targeted CNS-penetrant treatment options and the wide-field radiation required for leptomeningeal disease (CASE 5-2). Asymptomatic and paucisymptomatic patients may be particularly appropriate candidates for starting systemic treatment before proceeding with radiation therapy, but this decision depends on the type of cancer and the directed treatment options available and requires multidisciplinary input.[86] Symptomatic, rapid, and bulky growth typically requires immediate radiation for palliation of symptoms, with initiation of appropriate systemic treatment immediately thereafter. Symptomatic leptomeningeal disease involving the spinal cord, cauda equina, or nerve roots may be treated with focused lumbosacral radiation therapy which can help preserve or recover function. For symptomatic patients with leptomeningeal disease involving the brain or skull base, whole-brain radiation therapy may control symptoms and delay progression.

Craniospinal photon irradiation of the entire neuraxis is typically not recommended considering the high risk of severe treatment-related toxicity that occurs in almost one-half of patients, including fatigue, nausea, cognitive impairment, and perhaps most importantly bone marrow suppression that

Select Intrathecal Therapy Options for Patients with Leptomeningeal Disease[a] TABLE 5-1

Agent	Description	Half-life in cerebrospinal fluid	Recommended schedules of administration	Recommended prophylaxis for adverse events
Cytarabine	Pyrimidine nucleoside analogue	<1 hour	10 mg twice weekly (total 4 weeks), then 10 mg once weekly (total 4 weeks), then 10 mg once monthly	None
Liposomal cytarabine[b]	Pyrimidine nucleoside analogue	14 to 21 days	50 mg every 2 weeks (total 8 weeks), then 50 mg once monthly	Oral steroids[77]
Methotrexate	Folate antimetabolite	4.5 to 8 hours	10 mg to 15 mg twice weekly (total 4 weeks), then 10 mg to 15 mg once weekly (total 4 weeks), then 10 mg to 15 mg once monthly	Folinic acid rescue[78]
ThioTEPA	Alkylating ethyleneimine compound	3 to 4 hours	10 mg once every other week	Coadministered with methylprednisone 40 mg every other week[81]
Topotecan	Topoisomerase 1 inhibitor	1.3 hours[79,80]	0.4 mg twice weekly for 4 to 6 weeks, then weekly for 4 weeks, then biweekly for 4 weeks, then monthly	None
Trastuzumab	HER2-binding monoclonal antibody		80 mg twice weekly or 150 mg weekly	None[81,82]

[a] Modified from Le Rhun E, et al, Ann Oncol.[70] © 2017 European Society for Medical Oncology. Published by Elsevier Ltd.
[b] Currently not commercially available.

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KEY POINTS

- In a prospective randomized clinical trial, proton beam craniospinal irradiation has been shown to improve survival in patients with leptomeningeal disease as opposed to traditional photon beam radiation therapy.
- Health care disparities should be considered in the setting of CNS metastases, particularly with respect to the availability of stereotactic radiosurgery and proton beam radiation.

limits subsequent systemic therapy as a result.[87-91] These significant quality-of-life–limiting toxicities must be taken into account when considering photon-based craniospinal irradiation, especially in the setting of an overall poor prognosis. Proton craniospinal irradiation has also been evaluated as a potentially less toxic option for patients with leptomeningeal disease in a 2021 randomized phase 2 study, which showed a significant improvement in the progression-free survival rate and overall survival rate as compared with conventional photon beam radiation with no increase in serious treatment-related adverse events and a lower likelihood of bone marrow toxicity, allowing for improved tolerability of subsequent systemic therapy.[88] It should be noted that this study compared different techniques of irradiation and different fields of irradiation, and further data are needed to further elucidate the role of proton craniospinal irradiation in the context of leptomeningeal disease.

HEALTH DISPARITIES

While there have been exciting advances in the treatment of CNS metastases, we must make these therapies available to all patients. Proton beam radiation could potentially change recommended care in leptomeningeal disease treatment; however, in the United States, there are only 40 proton centers, most of which are located in urban areas and academic institutions. With many patients living in rural areas or lacking the means to travel to these proton centers, potential health care disparities exist in who can access this treatment. Additionally, as novel drug therapies arise, discrepancies in country-to-country availability or insurance coverage may also give rise to disparities in access to medical therapeutics.

Beyond these potential therapeutic disparities, there are similar geographic disparities in access to trained specialists with neuro-oncologic expertise, often due to the cost of travel. As the availability of telehealth services continues to grow, these experts could reach wider national and even international patient populations.

CONCLUSION

CNS metastases are increasing in prevalence as systemic cancer therapies continue to improve along with improvements in brain metastasis and leptomeningeal disease diagnostics. Despite the improvement in cancer therapy, CNS metastases, namely brain parenchymal metastases and leptomeningeal disease, continue to be challenging diseases to treat. Novel drug development paradigms including targeted therapy, antibody-drug conjugates, immunotherapy, and novel drug administration show potential promise for improving disease control. Key stakeholders, from the FDA to the American Society of Clinical Oncology and EANO-ESMO, have fortunately taken notice of the needs of these patients, and efforts to expand research and clinical trials in this arena have increased. We anticipate that increased inclusion of CNS metastasis patients in clinical trials will aid our understanding and improve outcomes for patients of this disease in the future.[10]

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DISCLOSURE

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Skull Base Tumors

By Deborah A. Forst, MD; Pamela S. Jones, MD, MS, MPH

ABSTRACT

OBJECTIVE: **This article reviews the presenting features, molecular characteristics, diagnosis, and management of selected skull base tumors, including meningiomas, vestibular schwannomas, pituitary neuroendocrine tumors, craniopharyngiomas, chordomas, ecchordosis physaliphora, chondrosarcomas, esthesioneuroblastomas, and paragangliomas.**

LATEST DEVELOPMENTS: **Skull base tumors pose a management challenge given their complex location and, as a result, the tumors and treatment can result in significant morbidity. In most cases, surgery, radiation therapy, or both yield high rates of disease control, but the use of these therapies may be limited by the surgical accessibility of these tumors and their proximity to critical structures. The World Health Organization classification of pituitary neuroendocrine tumors was updated in 2022. Scientific advances have led to an enhanced understanding of the genetic drivers of many types of skull base tumors and have revealed several potentially targetable genetic alterations. This information is being leveraged in the design of ongoing clinical trials, with the hope of rendering these challenging tumors treatable through less invasive and morbid measures.**

ESSENTIAL POINTS: **Tumors involving the skull base are heterogeneous and may arise from bony structures, cranial nerves, the meninges, the sinonasal tract, the pituitary gland, or embryonic tissues. Treatment often requires a multidisciplinary approach, with participation from radiation oncologists, medical oncologists, neuro-oncologists, and surgical specialists, including neurosurgeons, otolaryngologists, and head and neck surgeons. Treatment has largely centered around surgical resection, when feasible, and the use of first-line or salvage radiation therapy, with chemotherapy, targeted therapy, or both considered in selected settings. Our growing understanding of the molecular drivers of these diseases may facilitate future expansion of pharmacologic options to treat skull base tumors.**

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Forst and Jones discuss the unlabeled/investigational use of bevacizumab for the treatment of vestibular schwannomas in the setting of *NF2*-related schwannomatosis and nivolumab and ipilimumab for the treatment of aggressive adenomas.

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INTRODUCTION

Tumors that arise from or involve the skull base are a heterogeneous group of tumors, ranging from commonly observed tumors, such as meningiomas (the most common nonmalignant central nervous system [CNS] tumors), vestibular schwannomas, and pituitary neuroendocrine tumors, to more rare lesions, including esthesioneuroblastomas and paragangliomas. Although skull base tumors have a wide variety of biological behavior, these tumors are often associated with

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significant morbidity given their proximity to cranial nerves, cerebral vasculature, and adjacent brain parenchyma. Although gross total resection of skull base tumors may be curative or at least confer a significant survival advantage, the extent of resection is often limited by the complex neuroanatomic location of these lesions. Radiation is often used in the management of tumors and may have benefits in the initial treatment and recurrent settings. Emerging characterization of genetic alterations underlying the pathobiology of these tumors is informing the development and testing of targeted therapies, which may alter future treatment for these varied disease entities.

This article reviews important diagnostic characteristics and treatment considerations for selected skull base tumors, as well as ecchordosis physaliphora, an important non-neoplastic entity (TABLE 6-1[1-18]). Updates on the pathologic classification of these entities, including defining histopathologic and molecular features where applicable, are also presented.

KEY POINTS

- Although many meningiomas are found incidentally through head imaging performed for other reasons, patients may present with headaches, seizures, vision changes, personality changes, loss of hearing, weakness, or difficulty with speech or swallowing.
- Grade 1 meningiomas of the skull base are enriched with specific driver genetic variations, notably *SMO* in olfactory groove meningiomas, as well as *PI3K*, *AKT*, *TRAF7*, and *POLR2A*.

MENINGIOMAS

Meningiomas represent the most common type of intracranial brain tumor, comprising more than one-third of all CNS tumors with an age-adjusted annual incidence in the United States of 9.5 per 100,000 people.[1] They are extra-axial tumors, predominantly slow growing and benign (CNS World Health Organization [WHO] grade 1), that are believed to originate from arachnoid cap cells; however, a minority of these tumors behave more aggressively (grades 2 and 3).[19] Although meningiomas can be located anywhere along the neuroaxis, 30% of tumors arise along the skull base.[2] The peak occurrence is in the sixth and seventh decades of life, with a median age of occurrence of 67 years.[1] They are more common in women than in men, at a rate of 2:1, with a peak ratio of 3.15:1 in premenopausal women compared with men in the same age range.[20] The lifetime risk of meningioma is 1%, and the only known environmental risk factor is a history of ionizing radiation exposure, which leads to a 6-fold to 10-fold increase in incidence. The main genetic risk factor for meningioma is *NF2*-associated schwannomatosis (NF2), previously known as neurofibromatosis type 2.

Clinical Presentation of Meningiomas

Although many skull base meningiomas are found incidentally through head imaging performed for other reasons, patients may present with symptoms, including headache, seizures, vision changes, personality changes, loss of hearing, weakness, or difficulty with speech or swallowing.

Meningiomas possess several characteristic imaging features that help distinguish them from other skull base lesions such as pituitary neuroendocrine tumors and vestibular schwannomas and allow for a presumed diagnosis based on imaging alone. On CT, distinguishing features include internal calcification of the mass and occasional bony invasion, hyperostosis of surrounding bone, or both. On gadolinium-enhanced T1-weighted MRI sequences, lesions will typically be homogenously enhancing, often with a dural tail that distinguishes meningiomas from other homogenously enhancing skull base lesions, as well as a sunburst pattern that shows dural vessel supply. T2-weighted MRI sequences may display a thin rim of T2 hyperintensity around the lesion that is consistent with a cerebrovascular cleft.

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Meningioma Pathology

Meningiomas are classified largely by histopathology, although modern advances in molecular genomics and methylation studies have revealed signature somatic genetic variations and methylation profiles that may enhance clinicians' ability to predict tumor behavior and alter treatment strategies. WHO CNS criteria include three grades of meningiomas, including 15 subtypes, whereby grade 1 lesions comprise 80% to 90% of all meningiomas, grade 2 comprise 10% to 20%, and grade 3 comprise less than 1% of meningiomas. Grade 1 tumors

TABLE 6-1 **Epidemiologic and Clinical Features of Selected Skull Base Tumors**

Skull base tumor type	Description	Annual Incidence	Median age (years)	Clinical features
Meningioma	Tumors arising from arachnoid cap cells within the meninges	9.5 per 100,000 people[a]; of these, 30% arise from skull base[1,2]	67[1]	Most common primary central nervous system tumor Higher frequency in females, Black people, and older patients[1] Risk increases with exposure to ionizing radiation
Vestibular schwannoma	Benign tumor arising from Schwann cells of cranial nerve VIII	1.52 per 100,000 people[a]	55-60[1,3,4]	Most commonly present with tinnitus and hearing loss May develop vertigo, cranial nerve V and VII palsies, and obstructive hydrocephalus[5] Incidence rises with increasing age Typically unilateral except in patients with *NF2*-associated schwannomatosis
Pituitary neuroendocrine tumor	Benign tumor arising from the anterior pituitary gland	4-7.5 per 100,000 people[a,6]	51[1]	May be hormone secreting or nonsecreting Prolactinoma is the most common subtype and can be treated with dopamine agonists May cause bitemporal hemianopsia from optic chiasm compression
Craniopharyngioma	Benign epithelial tumor arising from Rathke pouch remnants	0.19 per 100,000 people[a,1]	45[1]	Bimodal age distribution in the first through second and fifth through sixth decades of life Two main types: (1) adamantinomatous (occurs in all ages, associated with *CTNNB1* variations) and (2) papillary (primarily in adults, with frequent *BRAF* variations)[7]

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are benign and include 13 subtypes. Grade 2 tumors, which include two subtypes, remain benign but behave more aggressively, with faster recurrence. Concerning histopathologic findings include high cellularity, prominent nucleoli, sheetlike pattern of growth, and necrosis, and grade 2 tumors have at least three of these features in addition to mitoses, brain invasion, or both. Some grade 1 tumors betray their categorization and have faster growth and regrowth rates. Grade 1 with atypical features is a category aimed at capturing tumors with one to two suspicious histopathologic features that have been correlated with shorter

CONTINUED FROM PAGE 1754

Skull base tumor type	Description	Annual Incidence	Median age (years)	Clinical features
Chordoma	Slow-growing malignant tumor arising from notochord	Less than 0.2% of all intracranial tumors[8]	55[9]	Located along the anterior midline of the spine and skull; most common at the sacrum, 35% arise from the skull base Male predominance
Ecchordosis physaliphora	Benign notochordal remnant	2% of autopsy specimens	Congenital	Typically small and asymptomatic Diagnostically may be confused with chordoma
Chondrosarcoma	Malignant tumor arising from cartilage	0.15% of all intracranial tumors[10]	42.5[10]	Three grades by histology, with grade 1 most common at the skull base *IDH1* and *IDH2* variations present in 50% of skull base tumors
Esthesioneuroblastoma	Malignant tumor arising from olfactory epithelium	0.4 per 1 million people[11]	54[12,13]	Often present with nasal symptoms (epistaxis, rhinorrhea, obstruction) Central nervous system involvement by contiguous spread
Paraganglioma	Neuroendocrine tumors arising from chromaffin cells in sympathetic or parasympathetic ganglia[14]	1 per 1.3 million people[15]	Sixth decade[16]	In adults, 30-40% of paragangliomas are familial or hereditary[17] More common in women[15,18]

[a] Annual United States age-adjusted incidence.

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progression-free survival.[21] Grade 3 tumors are malignant tumors with high rates of mitoses and aggressive histologic features. Studies indicated that skull base meningiomas have a lower risk of CNS WHO grades 2 and 3 histology compared with meningiomas that are not skull base tumors.[22]

There is a growing focus on better understanding meningioma biology and behavior through studying tumor genetics and epigenetics. Grade 1 tumors of the skull base are enriched with specific driver variations, notably *SMO* in olfactory groove meningiomas, as well as *PI3K*, *AKT*, *TRAF7*, and *POLR2A*.[23,24] Investigation into targeted treatment with molecular agents is underway with a national phase 2 trial.[25] The genetic landscape of meningiomas has also been profiled according to DNA methylation patterns. Early studies indicate that meningioma behavior, including recurrence and prognosis, may be better predicted by methylation classification rather than by WHO grading, including identifying grade 1 tumors with a high risk of progression and grade 2 tumors with a lower risk of progression. Although this work is preliminary, improved methods for predicting meningioma behavior beyond the current WHO classification stand to greatly affect clinicians' ability to manage these common tumors.

Management of Meningiomas

Although the majority of meningiomas are slow growing and benign, location along the skull base can pose significant challenges to management, given the proximity to critical neurovascular structures. Overall, treatment options include observation, surgery, or radiation, either via fractionated radiation therapy or stereotactic radiosurgery. For asymptomatic lesions, there is no Class 1 evidence for guiding first-line management and short-interval serial imaging is often the preferred approach. Nevertheless, volumetric studies indicate that 2.6% to 40% of skull base meningiomas will ultimately grow or cause symptoms that require surgical intervention.[26] Given the critical structures surrounding or occasionally involving these tumors and the challenging surgical approaches required to treat them, determining the threshold at which to intervene for asymptomatic lesions is nuanced. Imaging characteristics like calcification, a finding highly correlating with slow-growing grade 1 tumors, may guide a clinician toward observation. However, the presence of bony erosion, brain edema, or both, even in the setting of a smaller lesion, may correlate with a more aggressive tumor and push clinicians to surgically intervene. Surgery for skull base meningiomas typically involves either a craniotomy with microscopic or endoscopic techniques. Meta-analysis has shown that endoscopic techniques do not offer a significant advantage over open craniotomy, and they may have higher rates of subtotal resection and postoperative CSF leak.[27]

For anterior skull base lesions of the olfactory groove region, concerning findings may include brain edema with changes in executive function. For planum and tuberculum sella lesions, patients often require formal neuro-ophthalmic testing to assess for optic nerve compression, chiasm compression, or both. Lateral skull base meningiomas or foramen magnum meningiomas may cause worsening balance, weakness, hearing loss, or trigeminal neuralgia. Patients with tumors near or abutting the cranial nerve VII and VIII complex should undergo formal hearing testing with audiograms. If lesions are symptomatic or growing, surgery is recommended for removal or

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debulking to alleviate, stabilize, or prevent neurologic impairment. It is rare for these lesions to be amenable to preoperative embolization.

Radiation treatment, either radiation therapy or stereotactic radiosurgery, can be performed as first-line treatment in asymptomatic or growing tumors with high rates of long-term tumor control. Adjuvant radiation therapy for grade 1 tumors may be used for subtotally resected skull base tumors to limit the risk of recurrence in a tumor that is otherwise surgically inaccessible or poses a future threat to neurologic function. Radiation therapy is used as adjuvant therapy following subtotal resection of grade 2 tumors, and it frequently can be used following gross total resection (CASE 6-1) given the high rate of recurrence with surgery alone. There is an ongoing randomized control trial of radiation therapy versus observation following gross total resection for grade 2 meningiomas that will hopefully provide Level 1 evidence for guiding management.[28] Radiation therapy is always recommended for grade 3 tumors, regardless of the extent of resection.

The role of systemic therapy in meningiomas is currently limited, although there is increasing interest in the role of targeted therapy and immunotherapy. Ongoing trials are examining the role of AKT and SMO inhibitors, which are targeted therapies for mutations that are common in skull base meningiomas.[25,29,30] A phase 2 trial of PD-1 inhibition with nivolumab showed no improvement in progression-free survival.[31] Trials with other immunotherapy agents are currently enrolling.

KEY POINTS

- Meta-analysis has shown that endoscopic technique does not offer a significant advantage over open craniotomy in the resection of meningioma, and it may have higher rates of subtotal resection and postoperative CSF leak.
- Patients with vestibular schwannomas most commonly present with unilateral sensorineural hearing loss and tinnitus and less frequently present with vertigo and imbalance. Patients with larger tumors may develop symptoms related to brainstem compression or hydrocephalus.

SCHWANNOMAS

Schwannomas are benign (CNS WHO grade 1) peripheral nerve sheath tumors arising from Schwann cells. They occur sporadically in 90% to 95% of cases, with prior exposure to ionizing radiation identified as an established risk factor.[17,32] In the minority of cases, schwannomas arise in the context of NF2,[33] in which patients have a pathogenic germline variation in *NF2*, or in schwannomatosis associated with pathogenic variants in *SMARCB1* or *LZTR1*.[17] Skull base schwannomas arise from cranial nerves; this section focuses on vestibular schwannoma, the most common of these tumors.

Overview and Presenting Features of Vestibular Schwannomas

Vestibular schwannomas, also commonly referred to as *acoustic neuromas*, are benign tumors (CNS WHO grade 1) arising from Schwann cells of the vestibulocochlear nerve (cranial nerve VIII), with an age-adjusted annual incidence in the United States of 1.52 per 100,000 people and a median age of onset in the sixth decade of life.[1,3,4] The incidence of vestibular schwannoma has increased, with an increase in age at diagnosis and a decrease in tumor size at diagnosis. These findings likely reflect detection biases related to improvements in the availability and quality of neuroimaging, leading to the detection of lesions at greater frequency and earlier in the disease course, and perhaps a lower threshold for obtaining neuroimaging in the setting of asymmetric hearing loss.[3]

Patients most commonly present with unilateral sensorineural hearing loss and tinnitus and less frequently present with vertigo and imbalance. Patients with larger tumors may develop symptoms related to brainstem compression or hydrocephalus.[5,32]

Imaging features may be helpful to differentiate vestibular schwannomas from meningiomas and epidermoid cysts, which together with vestibular

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schwannoma are the most common cerebellopontine angle masses.[34] On MRI, a vestibular schwannoma typically presents as a T1-hypointense, T2-hyperintense, nodular lesion in the internal auditory canal, with moderate to strong postgadolinium contrast enhancement.[5,34] Enhancement may be heterogeneous, and larger lesions may demonstrate areas of cystic change and hemorrhage.[5,34] Calcifications are common in meningiomas but generally absent in vestibular schwannomas. Epidermoid cysts are characterized by the absence of enhancement and the presence of diffusion restriction.[34,35]

CASE 6-1

A 65-year-old man presented to the emergency department after being found unconscious by friends. His recent history was notable for 2 years of progressive loss of smell and 6 months of worsening bifrontal headaches. On arrival, he was awake but confused and combative. Laboratory examination was notable for a serum lactic acid level of 2.7 mmol/L (normal range: 0.5 to 2.2 mmol/L). Head CT (FIGURE 6-1A) and subsequent contrast-enhanced brain MRI (FIGURE 6-1C and 6-1D) demonstrated a large, dural-based enhancing mass along the floor of the anterior cranial fossa, with associated mass effect and vasogenic edema affecting the bilateral frontal lobes, as well as hyperostosis of adjacent bone (FIGURE 6-1B). He was started on levetiracetam for seizure prophylaxis because of concern that a seizure may have caused his loss of consciousness. Dexamethasone was administered for symptomatic cerebral edema. He underwent bifrontal craniotomy with near-total resection of the tumor, with the extent of resection limited by encroachment on major cerebral blood vessels. Histopathology was consistent with a meningothelial meningioma, with increased cellularity, prominent nucleoli, and foci of spontaneous necrosis, consistent with meningioma, central nervous system (CNS) World Health Organization (WHO) grade 2. Molecular testing revealed an *AKT1* gene variation. He was treated with adjuvant radiation therapy, without complications. At follow-up 5 years posttreatment, brain MRI showed no evidence of meningioma recurrence.

COMMENT

This case illustrates important aspects of meningioma presentation and management. As seen in this case, patients often present in middle or older age, and may report gradual symptom progression, in light of the relatively slower growth that is typical of these tumors. Although surveillance alone is an appropriate consideration for patients who have undergone gross total resection of a CNS WHO grade 1 or 2 meningioma, this patient was treated with adjuvant radiation because the higher-grade histopathology and subtotal resection increased his likelihood of recurrence. *AKT1* variations, as found in this patient's tumor, are frequently reported in skull base meningiomas.[29,30] An ongoing clinical trial is evaluating the use of AKT inhibitors to treat these tumors at progression.[25]

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Management of Vestibular Schwannomas

Options for management of vestibular schwannomas include observation, surgery, and radiation therapy, with a variety of tumor-related and clinical factors contributing to management decisions, including the size of the lesion or mass, effect on adjacent structures, comorbidities, and patient symptoms, preference, and age.[5,34] For patients with incidentally identified, asymptomatic lesions, observation may be reasonable, with serial neuroimaging and audiologic evaluations. Although efforts to identify predictors of vestibular schwannoma

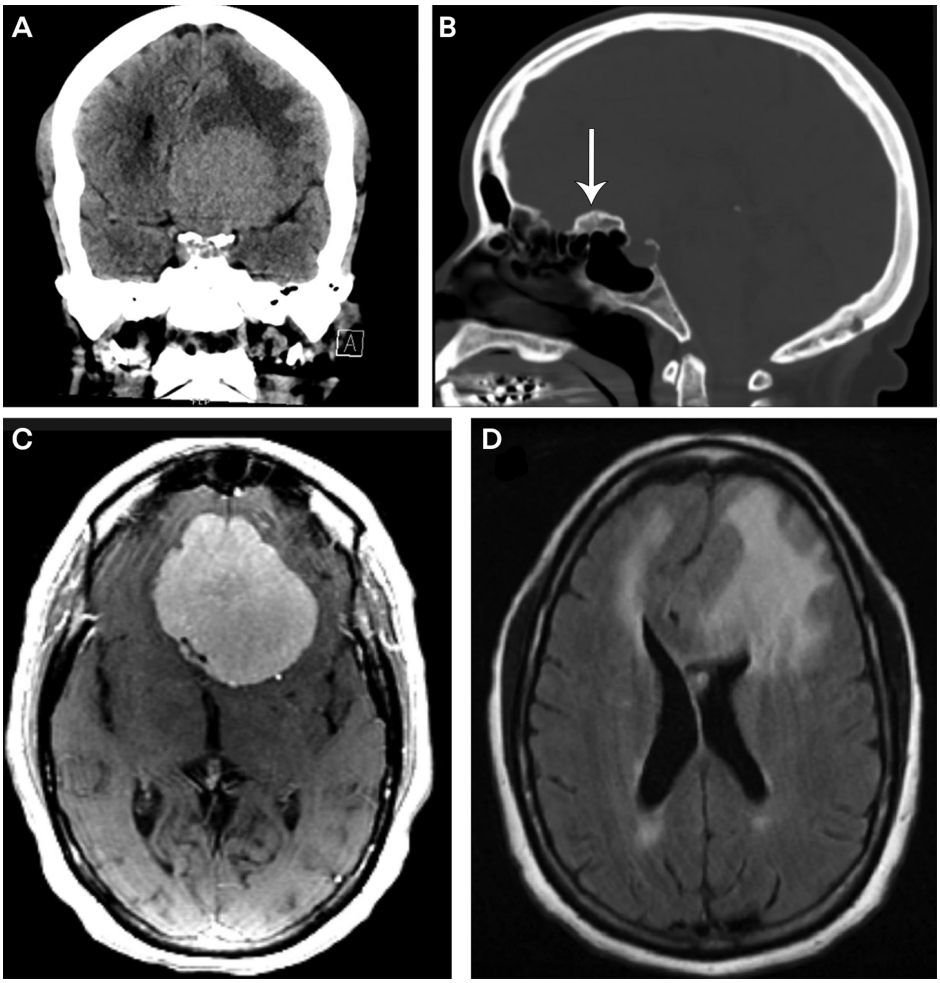

FIGURE 6-1

Brain imaging of the patient in CASE 6-1. At the time of presentation, the coronal noncontrast head CT image (*A*) revealed a hyperdense mass lesion along the anterior cranial fossa, with sagittal CT (*B*) that revealed hyperostosis of the adjacent bone (*arrow*). Subsequent axial T1-weighted MRI with gadolinium contrast (*C*) showed a homogeneously enhancing, dural-based mass, with corresponding axial fluid-attenuated inversion recovery (FLAIR) imaging (*D*) that demonstrated vasogenic edema affecting the left greater than right frontal lobes and significant mass effect on the brain parenchyma, with left-to-right midline shift.

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growth have yielded inconsistent findings, studies suggest that 25% to 50% of these tumors will grow over time, with a mean growth rate of 1 mm to 2 mm per year.[5,32]

For large or symptomatic lesions or cases of quickly growing tumors or progressive hearing loss, surgical resection is an important consideration.[36] With modern microsurgical techniques and selection of the optimal surgical approach (eg, translabyrinthine versus middle fossa craniotomy versus retrosigmoid approach), resection may be accomplished with attention to the preservation of

CASE 6-2

A 40-year-old man was brought to the emergency department with a 1-day history of severe headache, nausea, and vomiting. He had been in his usual state of health until 6 months before presentation, when he began to notice dull occipital headaches, which progressed in severity in the ensuing months, accompanied by right-sided tinnitus and episodes of vertigo. On initial examination, he appeared uncomfortable because of the headache and nausea but was otherwise in no evident distress. Neurologic examination was notable for torsional nystagmus with horizontal greater than vertical eye movements. Weber test resulted in lateralization of vibration better heard in the left ear. There were no other focal neurologic abnormalities. Brain MRI demonstrated a heterogeneously enhancing mass arising from the right internal auditory canal and measuring approximately 4 cm in maximum diameter (FIGURE 6-2A and 6-2B). There was significant mass effect on posterior fossa structures, with associated obstructive hydrocephalus (FIGURE 6-2C). He underwent suboccipital craniotomy with subtotal resection. A small amount of residual tumor was left on the cisternal portion of his right facial nerve (FIGURE 6-2D) because intraoperative monitoring indicated potential compromise of the nerve in that area and the risk of severe postoperative facial weakness. Pathology showed a vestibular schwannoma. The patient was subsequently monitored clinically and radiographically, with a plan to consider radiation therapy in the event of future recurrence.

COMMENT

This case highlights important considerations in vestibular schwannoma management. This patient presented with a symptomatic, large vestibular schwannoma and required surgical intervention to relieve tumor-associated mass effect and obstruction of CSF flow. Although radiation is an important tool in the management of vestibular schwannomas and may be considered as first-line therapy (in lieu of or following surgery) in selected cases, patients with large masses, progressive tumors, or symptomatic lesions may be considered for surgical resection. In this patient, a small amount of residual tumor was deliberately left behind to avoid damage to the facial nerve. This is particularly relevant because postoperative or iatrogenic facial paralysis is a source of great morbidity in patients who undergo vestibular schwannoma resection, with significant physical and psychological consequences in the event of severe postoperative facial paralysis.[36,37]

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facial function, and occasionally hearing can also be maintained in patients with smaller tumors.[36] This is particularly important as postoperative facial paresis remains the greatest source of postoperative morbidity for these patients,[36,37] as highlighted in CASE 6-2.

Stereotactic radiosurgery or radiation therapy, depending on tumor size, results in effective tumor control for the majority of patients, with stereotactic radiosurgery resulting in 5-year disease control rates of 90% or greater. For lesions smaller than 3 cm, some studies suggest stereotactic radiosurgery may be

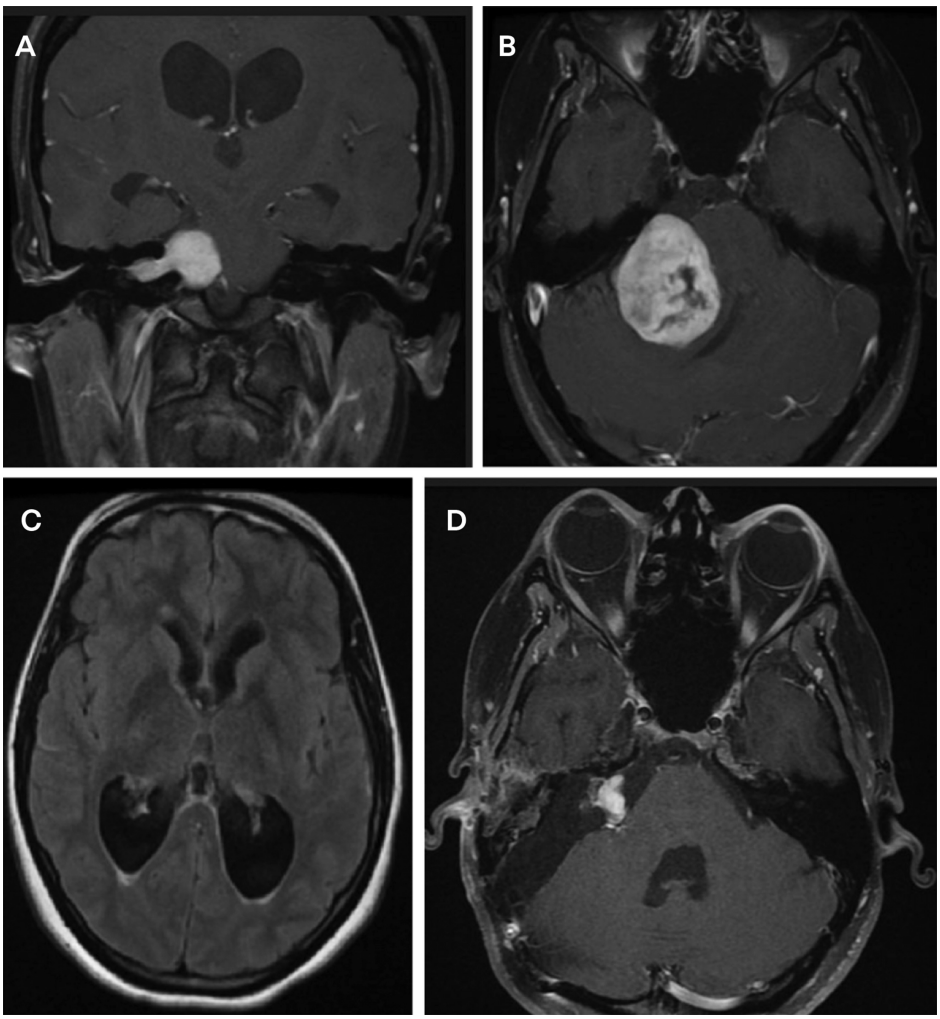

FIGURE 6-2

Brain imaging of the patient in CASE 6-2. Coronal postcontrast T1-weighted brain MRI (*A*) obtained at presentation shows a large mass lesion emanating from the right internal auditory canal, with heterogeneous enhancement and mass effect on the brainstem and cerebellum (*B*). On axial fluid-attenuated inversion recovery (FLAIR) images, there is dilation of the third and lateral ventricles (*C*), consistent with obstructive hydrocephalus. Axial postcontrast T1-weighted imaging from the postoperative MRI (*D*) demonstrates a small amount of residual tumor adherent to the cisternal portion of the right facial nerve.

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superior to surgery for hearing and facial function preservation, whereas other studies show that longer-term rates of hearing preservation may be similar between stereotactic radiosurgery and microsurgery.[5] Although stereotactic radiosurgery may induce a transient increase in lesion size in up to 30% of patients, a phenomenon known as pseudoprogression, there is thought to be minimal risk of malignant transformation of vestibular schwannoma after stereotactic radiosurgery.[5,38]

Prior and ongoing investigations have explored various targeted therapies, which may be used in the pharmacologic management of vestibular schwannoma, particularly in the setting of NF2.[39] Bevacizumab, an anti–vascular endothelial growth factor (VEGF) monoclonal antibody, has demonstrated benefit in tumor size reduction and hearing improvement in patients with NF2, and it is thus frequently given as an off-label treatment in this setting.[40,41]

PITUITARY NEUROENDOCRINE TUMORS

Pituitary neuroendocrine tumors, commonly known as pituitary adenomas, are benign tumors that arise from the anterior pituitary gland and are the third most common intracranial tumors after meningiomas and gliomas.[1] Tumors occur at an age-adjusted annual incidence in the United States of 3.9 to 7.4 per 100,000 people, with a median presenting age of 51 years.[1] The tumors are more frequent in females and have a higher incidence in Black people as compared with White people.[6] Despite the frequency of pituitary neuroendocrine tumors, there is no known environmental risk factor for tumor development. Although about 95% of tumors arise because of sporadic genetic variations, rare genetic risk factors for tumor development include multiple endocrine neoplasia types 1 and 4, familial isolated pituitary adenomas with *AIP* variation, and X-linked acrogigantism.[6]

Clinical Presentation of Pituitary Tumors

Pituitary neuroendocrine tumors have a variety of presentations depending on tumor size and the presence or absence of hormone secretion. Non–hormone-secreting tumors, known as nonfunctioning tumors, can be found incidentally on head imaging with relatively high frequency. In fact, incidentally discovered nonfunctioning adenomas may be found in up to 10% of MRI studies.[42] When nonfunctioning tumors lead to symptoms, patients typically present because of problems from tumor mass effect, which can lead to vision abnormalities including bitemporal field defects from optic chiasm compression, or because of hormone dysfunction or hypofunction from compression of the surrounding gland, which may involve symptoms such as fatigue, weight change, and sexual dysfunction.

Patients with pituitary neuroendocrine tumors that secrete a functioning hormone present with symptoms dependent on the hormone in excess. Prolactinomas, typically diagnosed when serum prolactin levels are greater than 200 ng/mL, are the most common pituitary neuroendocrine tumors overall. They present more frequently in women compared with men, with a rate of 10:1 during peak years of presentation (20 to 50 years).[43] Because of the excess production of prolactin, pituitary neuroendocrine tumors cause infertility, with either loss of menses and galactorrhea (women) or loss of libido and erectile dysfunction (men), and lead to inhibition of estrogen and testosterone. Growth hormone-secreting pituitary neuroendocrine tumors in adults lead to acromegaly and are the second most common functioning tumor. Patients may present with

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hand, foot, and jaw enlargement, coarsening of features, joint pain, acne, diabetes, and cardiovascular disease, among many other symptoms. Patients will have elevated insulinlike growth factor 1 levels and will fail an oral glucose tolerance test, whereby growth hormone does not suppress to less than 1 ng/dL. Adenomas producing an excess of adrenocorticotropic hormone (ACTH) represent the third most common functioning tumor, resulting in a syndrome known as Cushing disease. The characteristic presentation of these patients includes centripetal weight gain with wasting of the limb musculature, dorsocervical and supraclavicular fat pads, rounding of the face with plethora, diabetes, and cardiovascular disease, among other symptoms. Diagnosis of Cushing disease can be challenging because tumors are often small or even invisible on MRI. On biochemical testing, in addition to normal to elevated ACTH levels, patients have elevated late-night salivary cortisol levels, elevated 24-hour urine cortisol levels, and serum cortisol levels that do not decrease in response to low-dose overnight dexamethasone suppression testing. Finally, pituitary neuroendocrine tumors with secretion of thyroid-stimulating hormone (TSH) are quite rare but should be suspected in patients with typical symptoms of hyperthyroidism, including heart palpitations, tremors, and heat intolerance.

Rarely, functioning or nonfunctioning pituitary tumors may undergo spontaneous hemorrhage or infarction, known as pituitary apoplexy. With an incidence of 0.17 episodes per 100,000 people per year, these patients may present acutely with abrupt onset of severe headache alongside possible symptoms of nausea, vomiting, vision or ocular movement impairment, and altered level of consciousness. These presentations may be surgical emergencies, especially in cases of optic nerve or chiasm compression, although observation and supportive care has also been shown to lead to similar clinical outcomes. Acute adrenal insufficiency is the most life-threatening feature of pituitary apoplexy, and therefore urgent corticosteroid administration is warranted in all cases.

Pituitary Tumor Pathology

The WHO classification of pituitary neuroendocrine tumors was updated in 2022 with a focus on classifying tumors by both hormone staining pattern and transcription factor lineage.[44] By hormones, tumors are classified as somatotrophs (growth hormone), lactotrophs (prolactin), mammosomatotrophs (prolactin and growth hormone), thyrotrophs (TSH), corticotrophs (ACTH), and gonadotrophs (follicle-stimulating hormone and luteinizing hormone). There are also null cell tumors, which do not stain for any hormone, and plurihormonal tumors, which include multiple combinations of hormone staining in a monomorphous tumor population. These hormone types can be grouped by the presence of different transcription factors, which include PIT1 (somatotrophs, lactotrophs, mammosomatotrophs, and thyrotrophs), TPIT (corticotrophs), and SF-1 (gonadotrophs). Transcription factor staining has become commonplace for reporting in pituitary neuroendocrine tumor pathology and, with the updated 2022 criteria, it is now required.

As for determining tumor behavior, unlike many other CNS tumors, pituitary neuroendocrine tumors are not graded by aggressiveness. Studies have found that standard metrics like Ki-67 do not adequately predict tumor recurrence or invasiveness.[45] Pituitary neuroendocrine tumors are therefore divided into subtypes described by patterns of hormonal staining, whereby sparsely

KEY POINTS

- For vestibular schwannomas smaller than 3 cm, some studies suggest stereotactic radiosurgery may be superior to surgery for hearing and facial function preservation, whereas other studies show that longer-term rates of hearing preservation may be similar between stereotactic radiosurgery and microsurgery.
- Incidentally discovered nonfunctioning pituitary adenomas may be found in up to 10% of brain MRI studies.
- Studies have found that standard metrics like Ki-67 do not adequately predict pituitary neuroendocrine tumor reoccurrence or invasiveness.

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granulated patterns of staining for somatotrophs and corticotrophs portend a more aggressive course. However, sparsely granulated lactotrophs tend to be slow growing and are medically responsive, but they can behave aggressively in male patients. Densely granulated lactotrophs are rare and typically aggressive.[44] Of the nonfunctioning tumors, silent corticotrophs present without a diagnosis of Cushing disease on biochemical testing but stain for ACTH or TPIT, and these tumors pose a greater risk for aggressive behavior than standard nonfunctioning tumors.[46]

Management of Pituitary Tumors

As with the benign skull base tumors previously discussed, management options for pituitary neuroendocrine tumors involve observation, surgery, and radiation. The main exception to this is treatment for prolactinomas for which recommended therapy involves medical management with dopamine agonists. Once a sellar lesion is identified on MRI, patients are recommended to undergo endocrinologic workup to assess anterior pituitary gland function and tumor hormone status to inform the next steps of proper management. A typical serum hormone panel includes prolactin, growth hormone, insulinlike growth factor 1, TSH, free thyroxine, luteinizing hormone, follicle-stimulating hormone, ACTH, and fasting morning cortisol. This standard panel will signal any hyperfunction or hypofunction of the gland and any tumor secretion. Cushing disease requires further testing with urine and salivary cortisol levels for diagnostic confirmation. In addition to hormonal workup, patients with tumors that are larger than 1 cm (macroadenoma) and growing toward the optic nerves are recommended to undergo neuro-ophthalmic evaluation with formal visual field testing and optic coherence tomography to evaluate the health of the optic nerve.

For nonfunctioning tumors, observation is typically favored for tumors that are smaller than 1 cm (microadenoma) in maximum size. Surgery may be considered for macroadenomas that are growing or already approaching or compressing the optic nerves. Surgery is definitely warranted for tumors causing visual field deficits or optic nerve injury. The majority of pituitary tumors are removed via the endonasal transsphenoidal method, either with microscopic or endoscopic techniques. Decompression of the optic apparatus leads to high rates of visual recovery.[47] This point is well demonstrated by CASE 6-3.

For functioning pituitary neuroendocrine tumors other than prolactinomas, surgical excision is typically the first-line treatment regardless of tumor size. Growth hormone-secreting tumors are often macroadenomas and can be invasive into parasellar regions like the cavernous sinus. ACTH-secreting tumors, however, are microadenomas in 90% of patients, and up to 50% of the time they may be undetectable on standard MRI. When tumors are undetectable on MRI but patients are presumed to have ACTH-dependent hypercortisolemia, the next step in standard practice is to obtain an inferior petrosal sinus sampling to assess for a central (pituitary) rise in ACTH as opposed to a peripheral elevation. If the central-to-peripheral ratio is greater than 3:1 after stimulation with corticotropin-releasing hormone or, in some centers, desmopressin, then transsphenoidal surgery is recommended for exploration of the pituitary gland for a presumed ACTH-secreting adenoma.

Prolactinomas are typically managed with dopamine agonists such as cabergoline or bromocriptine, which shrink the tumor and normalize prolactin

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levels. Surgery is reserved for prolactinomas that are medication-resistant or for patients who are either intolerant of medication or for whom medication is contraindicated because of a history of psychiatric disease.

After surgical resection, long-term outcomes for patients with pituitary neuroendocrine tumors are favorable because of the low morbidity of surgery, high rates of vision improvement, and often slow growth of any residual tumor.[51] Tumors that undergo gross total resection as gauged by MRI have a 10% risk of recurrence at 5 years, so serial imaging is recommended. A small amount of residual tumor (less than 1 cm) may be monitored and further treated with radiation therapy if growth is observed. If the tumor is known to be recurrent or if large amounts of the tumor are unresectable, radiation may be pursued after surgery before further growth can occur. For patients with acromegaly or Cushing disease, surgery can result in biochemical remission, but if the tumor is invasive or unable to be totally removed, medical management, radiation following surgery, or both may be required for biochemical control. For the rare aggressive tumor, temozolomide therapy is currently the only recommended therapy after failure of surgery and radiation and is found to be effective for tumor control in one-third of patients.[52] There are limited data on the efficacy of targeted agents such as tyrosine kinase and mammalian target of rapamycin (mTOR) inhibitors for the treatment of pituitary tumors. There is interest in the role of immunotherapy for aggressive and metastatic pituitary neuroendocrine tumors because of the presence of tumor-infiltrating lymphocytes and programmed death-ligand 1 and programmed death-ligand 2 staining.[52,53] A phase 2 trial of the use of nivolumab and ipilimumab for the treatment of aggressive adenomas is underway.[54]

KEY POINT

- Pituitary neuroendocrine tumors that undergo gross total resection as gauged by MRI have a 10% risk of reoccurrence at 5 years, so serial imaging is recommended.

CRANIOPHARYNGIOMAS

Craniopharyngiomas are benign tumors of embryonic origin, arising from remnants of the Rathke pouch epithelium, from the sella turcica to the third ventricle.[7,55] There are two main types of craniopharyngiomas: adamantinomatous craniopharyngiomas and papillary craniopharyngiomas. The median age at diagnosis is 45 years, although there is a bimodal distribution, with cases peaking in the first through second decades of life and in the fifth through sixth decades of life.[1,7,56] Craniopharyngiomas occur with equal frequency in males and females.[17]

Presenting Features of Craniopharyngiomas

Adamantinomatous craniopharyngiomas, by far the more prevalent craniopharyngioma subtype, occur in both children and adults, demonstrating the aforementioned bimodal age distribution, and are characterized by *CTNNB1* variations (β-catenin variant).[7,17] Papillary craniopharyngiomas generally occur in adults and typically harbor $BRAF^{V600E}$ variations, resulting in activation of the mitogen-activated protein kinase pathway.[7,17] Patients may present with endocrinopathies, headaches, and visual disturbances, and presenting symptoms may vary by tumor location, with prechiasmal tumors often manifesting with visual symptoms (classically bitemporal hemianopsia due to compression of the optic chiasm), retrochiasmal tumors often presenting with hydrocephalus and associated symptoms of increased intracranial pressure, and sellar tumors frequently leading to endocrine dysfunction and headaches.[56,57]

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CASE 6-3

A 55-year-old woman presented to her primary care physician with a 3-week history of headache and blurring of her peripheral vision. On further questioning, she noted several weeks of prominent fatigue, new-onset constipation, and dry skin. She was referred for an ophthalmic evaluation during which formal visual field testing showed bitemporal hemianopsia (FIGURE 6-3). Brain MRI was obtained (FIGURE 6-4A and 6-4B) and demonstrated a heterogeneously enhancing sellar mass displacing the optic chiasm. Bloodwork revealed low levels of thyroid-stimulating hormone (TSH) and free thyroxine, consistent with central hypothyroidism, as well as low levels of adrenocorticotropic hormone (ACTH) and cortisol, consistent with central adrenal insufficiency. The patient was started on levothyroxine and prednisone. She underwent successful endoscopic transsphenoidal resection of the mass, with pathology that showed an adenoma, with tumor cells that stained diffusely positive for ACTH and TPIT. Findings were consistent with a nonfunctioning or "silent" corticotroph adenoma. Postoperatively, the patient developed polyuria and polydipsia and was found to have a serum sodium level of 154 mmol/L (normal range: 135 mmol/L to 145 mmol/L) with urine osmolality of 140 mOsm/kg (normal range: 150 mOsm/kg to 1150 mOsm/kg). She was diagnosed with central diabetes insipidus and started on desmopressin treatment. No further tumor-directed therapy was recommended, but serial brain and pituitary imaging for surveillance was planned. Follow-up MRI 1 year after surgery (FIGURE 6-4C) showed expected postsurgical changes, with no evidence of recurrent adenoma.

COMMENT

This patient presented with bitemporal hemianopsia secondary to a pituitary macroadenoma. Bitemporal hemianopsia suggests an injury to the optic chiasm, most commonly caused by a sellar or suprasellar mass lesion,[48] and warrants urgent brain imaging for evaluation. Pituitary adenomas, which are the most common type of sellar mass in adults, often present with headache, visual complaints, and hormone dysfunction, all of which were experienced by this patient. Pituitary adenomas are characterized by the presence or absence of excess hormonal activity; adenomas without excess hormone secretion are referred to as silent or nonfunctioning adenomas, and they account for 22% to 54% of all pituitary adenomas.[49] The most common type of nonfunctioning pituitary adenoma is a gonadotroph adenoma. The patient in this case was found to have a silent corticotroph adenoma, the second most common type of nonfunctioning pituitary adenoma.[49] Surgical resection of nonfunctioning pituitary adenomas may be curative, with progression-free survival rates between 80% and 90% at 5 years after resection, and 70% at 10 years.[50]

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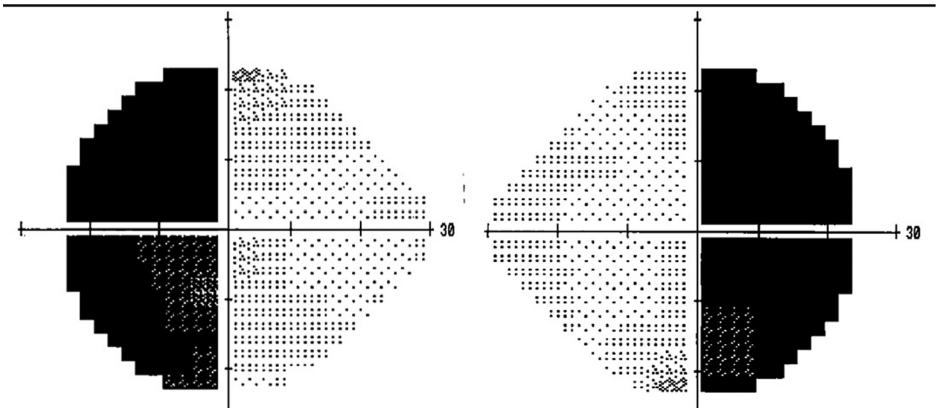

FIGURE 6-3
Visual fields of the patient in CASE 6-3 with pituitary macroadenoma. Preoperative visual fields show dense bitemporal field cuts.

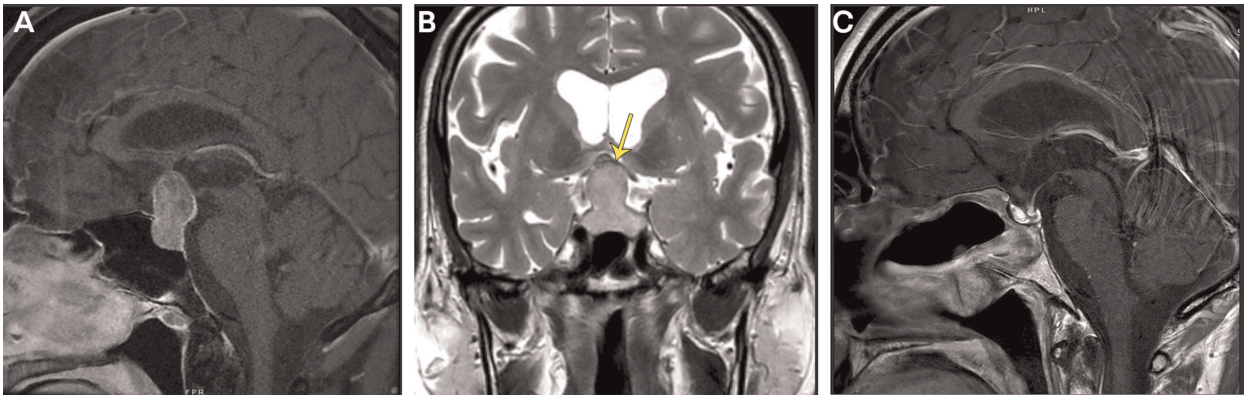

FIGURE 6-4
Neuroimaging of the patient in CASE 6-3 with pituitary macroadenoma. Preoperative sagittal T1-weighted brain MRI (*A*) with contrast demonstrates a heterogeneously enhancing sellar mass lesion, with displacement of the optic chiasm apparent on coronal T2-weighted imaging (*B, arrow*). On the 1-year postoperative follow-up sagittal T1-weighted brain MRI (*C*) with contrast, there is no evidence of tumor recurrence.

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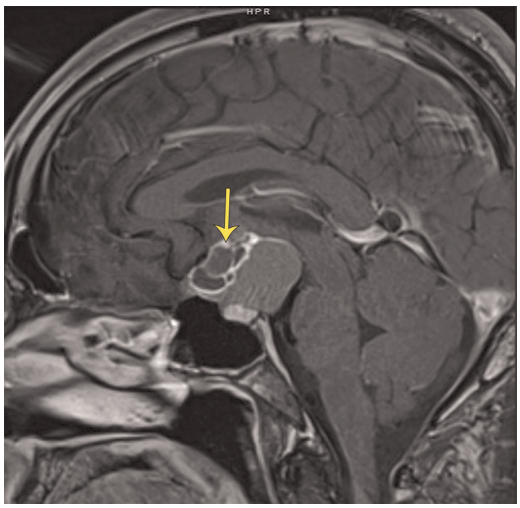

FIGURE 6-5

Brain MRI of a patient with an adamantinomatous craniopharyngioma. Sagittal postcontrast T1-weighted image shows a mixed solid and cystic suprasellar mass lesion with peripheral enhancement (most notably around the cystic areas) (*arrow*). The cyst contents display variable signal intensity, as is commonly seen with these lesions.

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On MRI, adamantinomatous craniopharyngiomas are typically mixed cystic and solid, multiloculated, and heterogeneous, with peripheral enhancement of cyst linings and areas of calcification.[7,58] The material within the cysts may have variable signal intensity (FIGURE 6-5), reflecting cholesterol, blood, and protein contents.[58] By contrast, papillary craniopharyngiomas typically lack calcifications and are primarily solid, at times with smaller cystic components.[7,58,59]

Management of Craniopharyngiomas

The management of adult patients with craniopharyngiomas typically involves maximum safe surgical resection, radiation therapy, or a combined approach. Surgical resection was historically associated with high morbidity, but the development of endoscopic endonasal approaches in lieu of transcranial microsurgical techniques has resulted in lower rates of perioperative morbidity and mortality and improved vision preservation.[56,60] Surgery may be useful in the reduction of mass effect on surrounding structures or cyst decompression and the establishment of a pathologic tissue diagnosis. However, whereas the reported rates of gross total resection with endoscopic endonasal approaches (37.5% to 91%) are greater than with transcranial approaches, the ability to achieve gross total resection of these tumors remains limited by the complicated location and their proximity to critical neurovascular structures, visual pathways, and endocrine structures.[60] Following gross total resection of a craniopharyngioma, observation may be considered. For patients undergoing subtotal resection, postoperative and adjuvant radiation therapy is thought to provide superior disease control compared with subtotal resection alone.[60,61]

To optimize the care of patients with subtotally resected tumors or recurrent tumors, there is a growing interest in the development and testing of targeted therapies. Given the prevalence of *BRAF*^{V600E} variations in papillary craniopharyngiomas, BRAF/MEK inhibitor therapy (eg, with vemurafenib and cobimetinib) is being tested in clinical studies, with preliminary results demonstrating high rates of treatment response.[62] For patients with adamantinomatous craniopharyngiomas, there is an interest in exploring inhibitors of the β-catenin/Wnt signaling pathway, although early reports of novel agents in this class raise concern for dose-limiting toxicities.[57] Other proposed signaling pathways that may be dysregulated in

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adamantinomatous craniopharyngiomas and serve as potential therapeutic targets include the sonic hedgehog, epidermal growth factor receptor, and VEGF signaling pathways.[57]

CHORDOMAS

Chordomas are rare and slow-growing tumors derived from embryonic remnants of primitive notochord that can arise anywhere along the midline of the anterior spine and skull. It is estimated that only 300 new patients are diagnosed each year in the United States. Chordomas present most commonly at the sacrum, but between 30% and 40% of these tumors are located at the skull base, arising from the clivus.[9] Clival chordomas represent less than 0.2% of all intracranial tumors. They can present at all ages, with an average age of diagnosis in the late fifties and a male predominance.[63]

Clinical Presentation, Diagnosis, and Management of Chordomas

Because of the proximity of clival chordomas to the brainstem, cranial nerves, and pituitary gland, these tumors can present with several symptoms, including intractable headache, cranial neuropathy, vision change, hormonal disturbances, and, rarely, CSF leak. Standard imaging findings include clival bony erosion on CT and an infiltrative mass on skull base MRI with the same signal intensity as surrounding tissue on T1-weighted images and hyperintensity on T2-weighted images.[64,65]

Diagnosis of chordoma is based on the pathologic specimen, and there are three histologic subtypes: (1) conventional, including the chondroid subtype, (2) poorly differentiated, and (3) dedifferentiated. Microscopically, chordoma is a moderately cellular tumor with physaliphorous (eg, bubbly appearing) cells containing intracytoplasmic mucin-laden vacuoles in a myxoid background. The presence of mitotic activity is rare in conventional chordomas, whereas poorly differentiated chordomas show high mitotic activity, high nuclear-to-cytoplasmic ratios, and prominent nucleoli. Poorly differentiated tumors typically present in children or young adults.[64] Immunohistochemistry shows staining for cytokeratin, S100, vimentin, and epithelial membrane antigen. Brachyury expression is a marker found distinctively in chordomas and can be used to pathologically distinguish them from similar appearing tumors like chondrosarcomas.[8]

Although these tumors are slow growing and histologically nonaggressive, they are challenging because of their locally destructive behavior invading bone and posteriorly through dura into the intracranial space, rendering them high risk for morbidity from both invasive and noninvasive treatments. Although there are no standardized management guidelines for chordomas, surgery for maximum safe resection is often the first-line treatment modality, when possible. Advances in technology with the use of endoscopes, neuronavigation, and neuromonitoring have allowed for expanded and safer access to clival chordomas, especially in centers with specialized skull base surgeons.[66] Nevertheless, most tumors cannot be cured with surgery alone. Adjuvant radiation is used for any unresectable, subtotally resected, or recurrent tumors, and it is commonly performed after gross total resection because of the survival benefit.[67] High-dose radiation (up to 70 Gy) with proton therapy is the favored approach over photon therapy, although there has been no randomized controlled trial comparing outcomes.[68]

KEY POINTS

- Given the prevalence of *BRAF*^{V600E} variations in papillary craniopharyngiomas, BRAF/MEK inhibitor therapy (eg, with vemurafenib and cobimetinib) is being tested in clinical studies, with preliminary results demonstrating high rates of treatment response.
- Brachyury expression is a marker found distinctively in chordomas and can be used to pathologically distinguish them from similar appearing tumors like chondrosarcomas.

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Systemic therapy is not used in the first-line management of chordoma, and tumors are largely resistant to traditional cytotoxic treatments when it is used in advanced metastatic cases. Targeted therapy with tyrosine kinase inhibitors and agents inhibiting the PI3K-mTOR pathway has been studied with some favorable results, although larger studies are needed.[8,69] Overall, even with aggressive surgical and radiation treatment, these tumors frequently reoccur, with 5-year overall survival and progression-free survival rates of 78.4% and 50.8%, respectively.[69]

ECCHORDOSIS PHYSALIPHORA

Ecchordosis physaliphora is a benign, congenital notochord remnant that warrants inclusion in this article given its potential diagnostic overlap with chordomas. This gelatinous, hamartomatous lesion is generally found at the dorsal clivus, to which it is attached by a bony or cartilaginous stalk.[70] Although the description of this as a clinical entity has historically largely been limited to case reports and small case series, autopsy series report the presence of ecchordosis physaliphora in up to 2% of autopsy specimens.[71–73]

Clinical Presentation, Diagnosis, and Management of Ecchordosis Physaliphora

Ecchordosis physaliphora is most commonly asymptomatic and thus found incidentally on CNS imaging obtained for unrelated symptoms; rarely, ecchordosis physaliphora may present with symptoms related to mass effect on neighboring structures.[71,73] Histopathologic features of ecchordosis physaliphora are identical to those of chordoma, with lesions characterized by physaliphorous cells in a myxoid stroma. Proposed criteria for immunohistochemical criteria include positive immunohistochemical stains for cytokeratins, epithelial membrane antigen, S100, galectin 3, and brachyury, consistent with notochord remnants, with absence of GFAP staining, demonstrating a lesion of nonglial origin.[73] Compared with chordomas, ecchordosis physaliphora lesions are more often hypocellular, with low proliferation rates and sparse pleomorphism, although these are nonspecific features.[71,73] As ecchordosis physaliphora cannot be reliably distinguished from chordoma by histopathologic features alone, the diagnosis hinges on the identification of common radiographic characteristics. Importantly, on MRI, ecchordosis physaliphora lesions are well-circumscribed dorsal and retroclival lesions that are hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging, demonstrate the absence of contrast enhancement, do not have bony erosion, and may have a T2 hypointense pedicle or stalk.[70,71] Expectant management is appropriate for asymptomatic ecchordosis physaliphora lesions, which may be followed with serial imaging, whereas symptomatic lesions may warrant surgical consideration.[73]

CHONDROSARCOMAS

Chondrosarcomas represent a rare malignant tumor type that arises from cartilaginous regions throughout the body, a subset of which arises along the lateral skull base. Because of the lateral location, tumors typically involve the cavernous sinus, the petrous bone, the sphenoid bone, or the clivus. They have a low incidence of disease, representing 0.15% of all intracranial tumors and, when combined with clival chordomas, represent 0.03 cases per 100,000 persons each

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year in the United States.[65] They are most frequently diagnosed in the fourth and sixth decades of life, with no sex predilection.[8,74]

Clinical Presentation, Diagnosis, and Management of Chondrosarcomas

Chondrosarcomas have similar clinical presentation to chordomas, including headache and cranial neuropathies, because of their similar location along the skull base and frequent involvement in the posterior fossa. On imaging, the tumors are expansile and show bony destruction, and a distinguishing feature of chondrosarcomas is often intratumoral calcification.[8] MRI findings between the chondrosarcomas and chordomas are similar, with intermediate-to-low signal on T1 sequences and high signal on T2 sequences; however, chondrosarcomas appear more laterally as opposed to midline.[8]

The pathologic diagnosis of chondrosarcoma is typically made based on tissue histology alone, although more recently molecular features of *IDH1* and *IDH2* variations have been found in half of these tumors in the skull base.[75] These tumors, although all malignant, have behavior that is delineated by three main histopathology subsets: (1) well-differentiated (grade 1), (2) moderately differentiated (grade 2), and (3) poorly differentiated (grade 3).[76] Grading is based largely on tumor cellularity, presence or absence of cartilage matrix, nuclear pleomorphism, and rate of mitoses. Skull base tumors are typically grade 1 and, rarely, grade 2. Histology shows a neoplasm composed of atypical chondrocytes with enlarged nuclei in a cartilaginous matrix, which differentiates these tumors from chordoma. Immunohistochemistry also helps distinguish these tumors from chordomas: although S100 protein is present in both tumors, chondrosarcomas do not express cytokeratin.[76] Genomic testing is commonly performed for these tumors because *IDH1* and *IDH2* variations are associated with longer progression-free and metastasis-free survival in high-grade chondrosarcomas.[77]

Like chordomas, typical recommended treatment includes maximum safe surgical resection followed by adjuvant radiation. Gross total resection of chondrosarcomas remains the therapeutic goal, but at the skull base location, proximity to critical neurovascular structures and possible bony invasion often limit the extent of safe tumor resection. Adjuvant high-dose radiation (up to 72 Gy) is used for residual tumors but, unlike in chordoma management, it is withheld in patients who have had gross total resection. Although advanced disease from chondrosarcomas is rare, the tumors are largely resistant to chemotherapy and targeted treatments. Long-term control for chondrosarcoma following radiation therapy is favorable, with 10-year local control and survival rates as high as 98% and 99%, respectively.[78]

ESTHESIONEUROBLASTOMAS

Esthesioneuroblastoma, also known as olfactory neuroblastoma, is a malignant neuroectodermal tumor of the sinonasal tract, originating from the olfactory epithelium; CNS involvement occurs through contiguous spread through the cribriform plate to involve the anterior cranial fossa, orbit, and brain.[11,79–81] This rare cancer represents 6% of sinonasal malignancies, with an estimated annual incidence of 0.4 per 1 million.[79,82] Esthesioneuroblastoma has a slight male predominance in some studies, and a bimodal age distribution, with one peak in patients 11 to 20 years old, but the highest incidence is in the sixth decade of life.[11,79,80]

KEY POINTS

- Targeted therapy of chordomas with tyrosine kinase inhibitors and agents inhibiting the PI3K-mTOR pathway have been studied with some favorable results, although larger studies are needed.
- Since ecchordosis physaliphora cannot be reliably distinguished from chordoma by histopathologic features alone, the diagnosis hinges on the identification of common radiographic characteristics.
- Genomic testing is commonly performed for chondrosarcomas because *IDH1* and *IDH2* variations are associated with longer progression-free and metastasis-free survival in high-grade chondrosarcomas.

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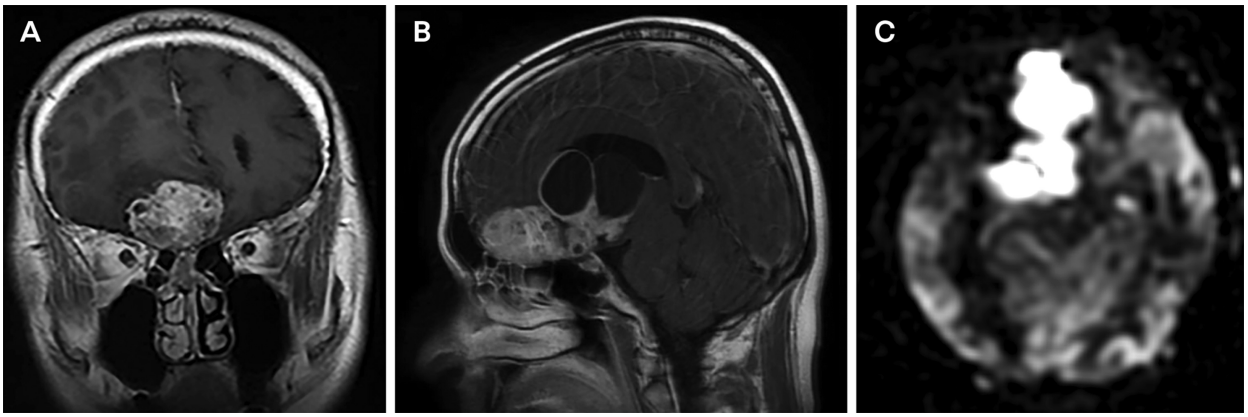

FIGURE 6-6
Brain MRI of a patient with esthesioneuroblastoma. Coronal (*A*) and sagittal (*B*) postcontrast T1-weighted imaging shows a heterogeneously enhancing mass with multiple cystic components centered in the cribriform plate with sinonasal and intracranial extension. Axial arterial spin labeling sequences demonstrate increased perfusion within the lesion (*C*), consistent with a neoplastic process.

Clinical and Radiographic Features of Esthesioneuroblastomas

Presenting symptoms of esthesioneuroblastomas commonly include anosmia, epistaxis, and nasal obstruction. Patients with orbital extension may experience proptosis, restricted eye movements, and visual symptoms. Up to 22% of patients may additionally have cervical lymphadenopathy at presentation, representing nodal metastases.[11]

CT features of esthesioneuroblastoma are nonspecific, with imaging that shows a soft tissue mass in the nasal vault, which may be accompanied by remodeling of adjacent bone or frank bony involvement and erosion.[83] On MRI, lesions typically are T1 hypointense or T2 intermediate to hyperintense, demonstrate contrast enhancement, and, in the context of intracranial extension, frequently display development of associated intracranial cysts (FIGURE 6-6).[83]

Diagnosis and Management of Esthesioneuroblastomas

As these tumors are amenable to direct endoscopic visualization, the initial step in diagnosis is generally endonasal biopsy.[84] The diagnosis hinges on the presence of characteristic histopathologic features, and although there are no pathognomonic immunohistochemical features, these tumors are generally positive for neuronal markers (eg, chromogranin, synaptophysin, neuron-specific enolase) and S100.[11,80] Esthesioneuroblastomas generally express somatostatin receptors. Tumors are graded from 1 to 4 based on histologic features using the Hyams grading system, which has demonstrated prognostic correlation.[11] Limited sequencing data shows a broad range of genetic alterations among tumor samples, although recurrent genetic variations were not commonly observed. The most frequently noted were *TP53* alterations, with studies suggesting potentially targetable alterations in the mTOR, CDK, and growth factor signaling pathways.[85,86] Some studies have reported the presence of pathogenic *IDH2* variations, and there is an emerging interest in the use of genome-wide DNA methylation profiles to aid in esthesioneuroblastoma classification.

Neck imaging should be performed as part of the workup, given the predilection of these tumors to metastasize to cervical lymph nodes.[83,84] The role of systemic

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imaging in evaluating for the rare occurrence of distant metastases is less well-established, but some advocate for obtaining fludeoxyglucose positron emission tomography (FDG-PET) or CT scans of the body. Alternatively, as esthesioneuroblastomas express somatostatin receptors, there is an emerging interest in the role of ^{68}gallium-dodecanetetraacetic acid tyrosine-3-octreotate PET in identifying metastatic foci.[87] Two systems for esthesioneuroblastoma staging, which may inform prognosis, have been proposed: the Kadish system and the Dulguerov system. The modified Kadish system is used most frequently and includes four stages (A-D), ranging from tumors confined to the nasal cavity (stage A) to those with regional lymph node involvement or distant metastases (stage D).[11,84]

The mainstay of treatment is aggressive surgical resection, including lymph node dissection in patients with cervical node involvement, followed by postoperative radiation therapy in most cases, except for patients with selected low-grade, early-stage lesions.[84] For advanced-stage and high-grade disease, neoadjuvant chemotherapy may be considered. There is an increasing interest in exploring the role of targeted therapies based on genomic profiling. Early reports show efficacy using peptide receptor radionuclide therapy (eg, lutetium Lu 177 dotatate) to treat patients with advanced disease, taking advantage of these tumors' somatostatin receptor overexpression as a molecular target.[82]

With aggressive treatment, the prognosis is generally quite good, with one series noting a 5-year disease-specific survival rate of 93.4%, with advanced Kadish stage, orbital invasion, intracranial invasion, and cervical lymph node involvement as negative prognostic factors.[88]

PARAGANGLIOMAS

Paragangliomas, also known as glomus tumors, are neuroendocrine tumors that arise from chromaffin cells in sympathetic or parasympathetic ganglia.[14] These rare tumors may involve the skull base, most commonly in the form of glomus jugulare, originating in the jugular foramen, or glomus tympanicum, arising from paraganglia associated with the inferior tympanic branch of the glossopharyngeal nerve.[89] Paragangliomas have an incidence of approximately 1 per 1.3 million people per year and occur more commonly in women in their fifth and sixth decades of life.[15,18]

Presenting Features of Paragangliomas

Clinical presentation varies by tumor location. Patients with glomus jugulare tumors may present with dysphagia, dysarthria, hypophonia, and weakness of the trapezius and sternocleidomastoid muscles because of the involvement of cranial nerves IX, X, and XI.[18] Glomus tympanicum may present with aural fullness, otalgia, hearing loss, or pulsatile tinnitus, with a reddish, pulsatile mass visible on otoscopy.[90] They are generally nonfunctioning, although between 1% and 3% of tumors may secrete catecholamines.[15] On MRI, glomus tumors characteristically demonstrate a salt-and-pepper appearance because of the presence of gadolinium contrast enhancement and flow voids.[91] In addition, glomus jugulare tumors may be associated with the widening of the jugular foramen, with or without bony erosion.[91]

Evaluation and Management of Paragangliomas

In adults, between 30% and 40% of paragangliomas are familial or hereditary, with pathologic germline variations identified in at least 17 genes; therefore, the

KEY POINTS

- Up to 22% of patients with esthesioneuroblastomas may additionally have cervical lymphadenopathy at presentation, representing nodal metastases.
- Limited sequencing data shows a broad range of genetic alterations among esthesioneuroblastoma samples, although recurrent variations are not commonly observed. The most frequently observed are *TP53* alterations, with recent studies suggesting potentially targetable alterations in the mTOR, CDK, and growth factor signaling pathways.
- There are early reports of efficacy using peptide receptor radionuclide therapy (eg, lutetium Lu 177 dotatate) to treat patients with advanced disease, taking advantage of esthesioneuroblastomas' somatostatin receptor overexpression as a molecular target.
- In adults, between 30% and 40% of paragangliomas are familial or hereditary, with pathologic germline variations identified in at least 17 genes to date; therefore, the evaluation of patients with paragangliomas should include a detailed family history and referral to a genetic counselor to discuss testing for a heritable genetic variation.

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evaluation of patients with paragangliomas should include a detailed family history and referral to a genetic counselor to discuss testing for a heritable genetic variation.[17,92] The optimal management of skull base paragangliomas is debated and may include surgery, radiation therapy, or observation. Although surgery has historically been the preferred treatment modality, it may be difficult to achieve a gross total resection, and aggressive surgical approaches may carry a risk of cranial nerve compromise.[90] Radiation therapy, particularly radiosurgery, results in high rates of disease control and may be considered as an alternative option to surgery, or it may be used in adjuvant or recurrent settings.[15,18,90] As the majority of skull base paragangliomas exhibit benign, indolent behavior, observation may be considered in selected patients.[90] Treatment decisions should incorporate input from multidisciplinary specialists and may be informed by patient age and comorbidities, tumor size, associated symptoms, cranial nerve involvement, and the presence or absence of catecholamine secretion.[90] In rare cases of advanced or metastatic paragangliomas, management options include systemic chemotherapy or treatment with iobenguane I 131 (radiolabeled metaiodobenzylguanidine) for metaiodobenzylguanidine-positive tumors.[93] Areas of ongoing investigation for advanced disease include targeted therapies, with initial promise seen in studies of the antiangiogenic tyrosine kinase inhibitors sunitinib and axitinib and interest in the potential use of hypoxia-inducible factor inhibitors and mTOR inhibitors; immunotherapy, including checkpoint inhibitors and vaccine therapy; and radiopharmaceuticals, including an ongoing clinical trial evaluating lutetium Lu 177 dotatate for inoperable paragangliomas with positive ^{68}gallium-dodecanetetraacetic acid tyrosine-3-octreotate PET.[93-95]

CONCLUSION

Skull base tumors are a heterogeneous group of tumors with a variety of clinical manifestations related to their effects on surrounding nerves, the brain, and the vascular supply. Surgery and, often, adjuvant radiation have been the mainstays of treatment, but they may be limited because of the morbidity of aggressive treatment in proximity to critical structures. On the horizon, the growing understanding of the molecular underpinnings of these tumors and the investigation of targeted therapies stand to greatly enhance the safe and effective management of these diseases.

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Paraneoplastic Neurologic Syndromes

By Jerome J. Graber, MD, MPH, FAAN

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **Progress is ongoing in understanding paraneoplastic neurologic disorders, with new syndromes and antibodies being described and more detailed evidence available to guide workup for diagnosis and treatment to improve outcomes. Many excellent reviews have summarized the molecular features of different antibodies, but this article emphasizes the clinical features of each syndrome that may help guide initial diagnosis and treatment, which often should occur before an antibody or cancer is found to confirm the diagnosis.**

LATEST DEVELOPMENTS: **Recent findings include updated diagnostic criteria with validated sensitivity and specificity, discovery of novel antibodies, and clinical findings that increase the likelihood of an underlying paraneoplastic disorder. Suggestive syndromes that have been recently identified include faciobrachial dystonic seizures and pilomotor auras in anti–leucine-rich glioma inactivated protein 1 encephalitis, extreme delta brush on EEG in *N*-methyl-D-aspartate (NMDA)-receptor encephalitis, déjà vu aura in anti–glutamic acid decarboxylase 65 (GAD65) encephalitis, and sleep disturbances in several disorders. In addition, there is confirmed utility of brain positron emission tomography (PET) and CSF markers, including carcinoembryonic antigen and oligoclonal bands, as well as improved tests for the presence of leptomeningeal cancer cells in CSF. Associations of cancer immunotherapies with paraneoplastic syndromes and herpes simplex virus encephalitis (and COVID-19) with NMDA-receptor encephalitis have been described.**

ESSENTIAL POINTS: **All neurologists should be aware of advances regarding paraneoplastic neurologic syndromes, as patients can present with a wide variety of neurologic symptoms and earlier diagnosis and treatment can improve outcomes.**

INTRODUCTION

Paraneoplastic disorders are rare, with approximate incidences of 0.8 to 0.89 per 100,000 person-years, 1 in 300 cancers, or 0.4 cases per 1,000,000 children in the case of opsoclonus-myoclonus syndrome. Case numbers have been slightly increasing since 2002, likely due to improved diagnostic methods.[1-3] In the California Encephalitis Project, *N*-methyl-D-aspartate (NMDA)-receptor encephalitis was more common than any other identifiable viral encephalitis in people under 30 years

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RELATIONSHIP DISCLOSURE:
Dr Graber has noncompensated relationships as a member of the board of directors of the American Society of Neuroimaging, a certification examination committee member with the United Council of Neurological Subspecialties, an editorial board member of the *Journal of Pain and Symptom Management*, *Neuro-Oncology: Practice*, and *Practical Neurology*, a member of the *Neurology* Question of the Day app committee, and a developer of NeuroSAE materials with the American Academy of Neurology (AAN) that are relevant to AAN interests or activities.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Graber discusses the unlabeled/investigational use of corticosteroids, cyclophosphamide, intravenous immunoglobulin, ixazomib, lenalidomide, plasma exchange, and rituximab for the treatment of paraneoplastic neurologic syndromes.

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TABLE 7-1 **2021 Updated Diagnostic Criteria for Paraneoplastic Neurologic Disorders**[a]

Criterion	Points	Examples
Clinical phenotype		
Phenotype with high risk of cancer association	3	Limbic encephalitis, encephalomyelitis, opsoclonus-myoclonus syndrome, rapidly progressive cerebellar syndrome, sensory neuronopathy, Lambert-Eaton myasthenic syndrome, gastrointestinal pseudo-obstruction
Phenotype with intermediate risk of cancer association	2	Encephalitis (not limbic), brainstem encephalitis, Morvan syndrome, stiff person syndrome, isolated myelopathy, polyradiculoneuropathies (not chronic inflammatory demyelinating polyradiculoneuropathy or Guillain-Barré syndrome unless a paraneoplastic antibody is found)
Phenotype not associated with cancer	0	All other clinical presentations
Laboratory testing		
Antibody with high risk of cancer association (>70%)	3	Antineuronal nuclear antibody type 1 (Hu), antineuronal nuclear antibody type 2 (Ri), Purkinje cell cytoplasmic antibody type 1 (Yo), Purkinje cell cytoplasmic antibody type 2, Ma, Kelch-like protein 11, Tr-delta/notch-like epidermal growth factor–related receptor, collapsin response mediator protein-5, amphiphysin, SRY-box transcription factor 1, *N*-methyl-D-aspartate (NMDA)
Antibody with intermediate risk of cancer association (30% to 70%)	2	α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), γ-aminobutyric acid B ($GABA_B$), metabotropic glutamate receptor 5, P/Q voltage-gated calcium channel, contactin-associated proteinlike 2 (CASPR2)
Antibody with lower risk of cancer association (<30%)	0	Metabotropic glutamate receptor 1, γ-aminobutyric acid A ($GABA_A$), CASPR2, glial fibrillary acidic protein, glutamic acid decarboxylase 65 (GAD65), leucine-rich glioma inactivated protein 1, dipeptidyl-peptidase–like protein 6, glycine receptor, aquaporin-4, myelin oligodendrocyte glycoprotein
Cancer or tumor		
Found and consistent with phenotype, antibody, or antigen	4	PCA-1 (Yo) and breast cancer; ANNA1 (Hu) and lung cancer
Not found or not consistent but <2 years follow-up	1	ANNA1 (Hu) and no cancer found on repeat screening; GAD65 and prostate cancer
Not found >2 years follow-up	0	
Diagnostic level	**Total points**	
Definite	8 or more	
Probable	6-7	
Possible	4-5	
Nonparaneoplastic	3 or less	

[a] Data from Graus F, et al, Neurol Neuroimmunol Neuroinflamm.[6]

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old.[4] These syndromes span the full spectrum of neurology from cognitive and encephalitic disorders to peripheral and neuromuscular syndromes and every part of the nervous system in between, challenging both general and subspeciality neurologists to recognize them in inpatient and outpatient settings. Many patients may not present to specialty centers and may not have access to specialist neuro-oncologists or neuroimmunologists.[5] Because early recognition and diagnosis can be critical for effective management, all neurologists and oncologists should be prepared to identify paraneoplastic disorders and initiate investigations. Diagnostic criteria updated in 2021 have been independently validated to demonstrate improved sensitivity and specificity.[6,7] These criteria use the Paraneoplastic Care Score to classify neurologic syndromes as definite, probable, possible, or nonparaneoplastic syndromes, based on the presence of high-risk, intermediate-risk, or low-risk phenotypes, antibodies, and cancer (notably requiring long-term follow-up with repeat evaluation for cancer) (TABLE 7-1[6]). In the early period of diagnosis, when treatment is most critical, this score is difficult to implement in situations of atypical syndromes while awaiting a cancer workup and antibody tests, which can take weeks, especially in the common situation where the initial cancer workup is negative. In addition, advanced cancer and antibody testing can be costly and difficult to obtain in the inpatient setting or resource-poor areas, especially for the most impaired patients.

This article explores various clinical syndromes and emphasizes those that are less rare, are amenable to treatment, or have a high incidence of associated cancer. It is important to remember that although various antibodies may cause overlapping or different clinical presentations, some paraneoplastic syndromes will not have an associated detectable antibody (TABLE 7-2[6]).

KEY POINT

- Although various antibodies may cause overlapping or different clinical presentations, some paraneoplastic syndromes will not have an associated detectable antibody.

CLINICAL EVALUATION OF PARANEOPLASTIC DISORDERS

Prodromal symptoms of paraneoplastic disorders are common but not universal, with 20% to 30% of patients having a fever, upper respiratory symptoms, or gastrointestinal symptoms shortly before neurologic symptom onset. This prodrome is characteristically followed by acute to subacute progression of neurologic symptoms, but 40% of patients do not recall any noticeable prodromal illness.[8] Interestingly, sleep disturbances such as insomnia, hypersomnia, and parasomnia are common in particular antibody syndromes (especially dream enactment in anti–leucine-rich glioma inactivated protein 1 [LGI1] encephalitis), which may supply a helpful clue. Polysomnography can also detect occult seizures including faciobrachial dystonic seizures and central sleep apnea.[9,10] A family history of autoimmune disease is more common in patients with paraneoplastic syndromes.[11] An underlying immunogenetic predisposition to paraneoplastic neurologic disorders may be present, as seen with human leukocyte antigen–type and immune gene associations for NMDA-receptor encephalitis.[12] This is most suggestive in syndromes with a low incidence of associated tumors: 90% of patients with IgLON family member 5 (IgLON5)-related syndromes have the DQB1*05 allele and 60% also have the DRB1*10:01 allele; 90% of patients with contactin-associated proteinlike 2 (CASPR2)-related syndromes have the DRB1*11:01 allele; and 40% of patients with glutamic acid decarboxylase 65 (GAD65)-related syndromes have the DQB*02:01 allele. However, no genetic human leukocyte antigen–type associations were found for anti–Purkinje cell cytoplasmic antibody type 1 (PCA-1) (Yo) antibodies and other paraneoplastic syndromes with a high

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incidence of tumors.[11] CSF markers of inflammation (eg, elevated white blood cell concentration, elevated IgG index versus serum, oligoclonal bands, 14-3-3 protein, elevated neurofilament light chains) are common but nonspecific, and they are absent in more than 20% of patients over 65 years old with paraneoplastic neurologic disorders and vary in different antibody disorders (abnormal in 90% of patients with NMDA, γ-aminobutyric acid B [$GABA_B$], and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid [AMPA] disorders, 40% of those with LGI1 disorders, and 20% of those with CASPR2 disorders).[13] In addition, CSF 14-3-3 protein is found in 12.5% of patients with paraneoplastic syndromes and some syndromes can overlap with Creutzfeldt-Jakob disease presentations, but patients with paraneoplastic syndromes show a double-banding pattern while patients with Creutzfeldt-Jakob disease have a single band.[14] A pattern of sudden worsening symptoms after tumor biopsy without resection may be related to a sudden spilling of tumor antigen or peritumoral inflammatory provocation and can be another clue in some cases.

Since confirmatory testing often takes weeks and paraneoplastic disorders are rare, it is important to quickly ensure that another mimic that requires urgent treatment is not responsible for the neurologic presentation, such as atypical stroke or vasculopathy, atypical infections, thiamine deficiency, or occult leptomeningeal metastases, all of which are more common in people with cancer. For example, herpes simplex virus (HSV) encephalitis appears to be more common in patients with cancer, especially those undergoing craniotomy or brain radiation therapy, occurring in as many as 1 out of 400 people undergoing brain radiation therapy, and is more likely to have an atypical presentation in patients with cancer with an absence of fever or CSF leukocyte elevation.[15] Thiamine deficiency (without the complete triad of ocular abnormalities, cerebellar ataxia, and memory impairment) also occurs with increased frequency

TABLE 7-2 **Neurologic Syndromes With High Risk of Paraneoplastic Cause**[a]

Syndrome	Antibodies	Tumor associations
Limbic encephalitis	Antineuronal nuclear antibody type 1 (ANNA1) (Hu), *N*-methyl-D-aspartate (NMDA) receptor, Ma, leucine-rich glioma inactivated protein 1	Breast, testes, ovaries, lung
Opsoclonus-myoclonus syndrome	Antineuronal nuclear antibody type 2 (Ri)	Neuroblastoma, breast, small cell lung cancer
Cerebellar syndromes (rapid onset)	Purkinje cell cytoplasmic antibody type 1 (Yo), Purkinje cell cytoplasmic antibody type 2, glutamic acid decarboxylase 65, voltage-gated calcium channel (VGCC)	Breast, ovaries, lung
Sensory neuronopathy	ANNA1 (Hu), collapsin response mediator protein-5	Small cell lung cancer
Lambert-Eaton myasthenic syndrome	P/Q VGCC	Small cell lung cancer
Gastroenteric pseudo-obstruction	ANNA1 (Hu), ganglionic acetylcholine	Breast
NMDA-receptor encephalitis	NMDA receptor	Teratoma

[a] Data from Graus F, et al, Neurol Neuroimmunol Neuroinflamm.[6]

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in people with cancer (especially gastrointestinal [GI] and hematologic malignancies), often without any history of alcohol use or overt malnutrition, and must be recognized and treated urgently.[16] Unfortunately, leptomeningeal metastases are common in this population and can mimic numerous paraneoplastic neurologic syndromes with normal MRI and CSF cytology and can cause unusual presentations with focal seizures, multiple cranial nerve palsies, spinal radiculopathies, and atypical hydrocephalus with "pressure waves" (ie, brief episodes of confusion or syncope associated with activities that raise intracranial pressure).[17,18] CSF flow cytometry, CSF carcinoembryonic antigen levels, and circulating tumor cell staining can increase detection in leptomeningeal hematologic tumors, and DNA sequencing can increase detection in leptomeningeal endothelial tumors. A 2023 retrospective series from several referral centers found that most patients misdiagnosed with autoimmune encephalitis had another common neurodegenerative disorder (eg, Alzheimer disease, dementia with Lewy bodies, or frontotemporal dementia) or psychiatric disorder (eg, depression) and did not meet full criteria for autoimmune encephalitis. Low-titer false-positive antibodies (eg, GAD, voltage-gated potassium channel) were a common contributor to misdiagnosis in this series.[19] See TABLE 7-3[20,21] for clues to mimics of paraneoplastic neurologic syndromes that require rapid diagnosis and treatment.

Once a paraneoplastic syndrome is suspected, it is important to obtain a thorough history including prodromal symptoms, risk factors for cancer, and autoimmunity in the patient and their genetic relatives; conduct a thorough physical examination including full skin, testicular, breast, and gynecologic examinations and full-body lymph node examination (especially supraclavicular lymph nodes); and then choose how to send serum and CSF for diagnostic tests. It is relatively straightforward to screen for underlying malignancy with CT scans of the chest, abdomen, and pelvis with and without contrast, but if they are unrevealing, it is harder to decide whether to proceed to more detailed screening including colonoscopy, mammogram, gynecologic or testicular ultrasound, or full-body positron emission tomography (PET); this is where symptomatic or risk factor clues to a particular organ site and serum tumor markers may be helpful. PET can be very helpful in detecting occult underlying malignancy (CASE 7-1) as well as demonstrate suggestive brain metabolic patterns of paraneoplastic syndromes (regional hypermetabolism) or potential mimics (regional hypometabolism), but PET can lead to false positives as well.[22–24] Certainly, if a syndrome with a high incidence of underlying tumor is strongly suspected or confirmed by antibody testing, or symptoms progress despite initial immune suppression, proceeding to PET (possibly a full-body scan including brain imaging) is appropriate and often very useful when antibody testing is negative but when a typical paraneoplastic syndrome with high tumor incidence is present.[24]

KEY POINTS

- CSF 14-3-3 protein is a nonspecific marker of neuronal injury and can be positive in prion diseases or paraneoplastic neurologic disorders.
- Ictal autonomic symptoms like gastrointestinal changes, piloerection, ictal fever, bladder sensations, or cough may be more common in antibody-associated epilepsies.
- Including the brain in positron emission tomography (PET) screening of the body for occult cancers can help diagnose paraneoplastic neurologic syndromes (eg, showing focal brain hypermetabolism).

PARANEOPLASTIC ENCEPHALITIS AND SEIZURES

Limbic encephalitides are some of the most commonly encountered paraneoplastic syndromes, with distinct clinical features that can provide clues to the underlying specific cause.

NMDA-Receptor Encephalitis

NMDA-receptor encephalitis may be one of the most common paraneoplastic neurologic syndromes, with incidence estimates of 1.5 cases per million people annually.[25] Ninety percent of patients have prominent acute or subacute onset of

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TABLE 7-3 **Mimics to Consider With a Potential Paraneoplastic Neurologic Disorder**

Mimic	Clues	Pitfalls	Diagnostic	Treatment
Leptomeningeal metastases	Rapidly progressive cranial and spinal nerve palsies with headaches or pain	MRI is negative in approximately 10% of biopsy or CSF-proven leptomeningeal metastases	Triple-dose gadolinium with thin cuts Cell-free DNA testing of CSF (can detect cytokeratin or other tumor marker expression with greater sensitivity than standard cytology)	Dependent on tumor type
Skull base metastases	Cranial nerve palsies, especially numb chin syndrome	"Negative" MRI (small bony lesions can be very difficult to appreciate on MRI) and CSF testing	Positron emission tomography/CT scan that includes the entire skull	Focal radiation and tumor directed
Herpes simplex virus and other encephalitis or subacute meningitis syndromes (eg, Whipple disease, human herpesvirus 6, tuberculosis, brucella)	Rapid onset after brain radiation or craniotomy	May lack fever or CSF leukocytosis; immune suppression worsens	In patients with herpes simplex virus encephalitis, MRI showing characteristic insular and temporal lobe lesions, CSF herpes simplex virus polymerase chain reaction	IV acyclovir for patients with herpes simplex virus encephalitis
Thiamine deficiency	Ocular motor abnormalities, gait dysfunction, memory impairment, malnutrition	Not always related to alcohol intake or malnutrition in patients with cancer	Laboratory testing is often delayed, treat presumptively	IV or IM thiamine
Nonconvulsive status	Stuttering course	More common in patients with cancer	Prolonged EEG monitoring	Antiseizure medications
Botulism	Ascending paralysis with pupillary paralysis	Testing can be challenging to obtain quickly	Botulinum toxin testing, electrodiagnostic testing	Antitoxin
Guillain-Barré syndrome	Rapid progression over days	CSF test results are nonspecific	Electrodiagnostic testing, 2.7% of patients will have cancer	Intravenous immunoglobulin (IVIg), plasma exchange, supportive care,
Myasthenic crisis	Rapid onset after neuromuscular blocking or immune checkpoint inhibitor treatment	Overlaps with paraneoplastic myasthenic syndromes	Confirmatory antibody or electrodiagnostic testing	Steroids, IVIg, plasma exchange

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Mimic	Clues	Pitfalls	Diagnostic	Treatment
Fluoroquinolone, opioid, or gabapentin toxicity	Myoclonic tremor and delirium after use of these medications	Can be subacute, more common in older adults and underweight patients, and those with hepatorenal dysfunction	Verify renal clearance and accurate dosing Improvement after holding or reducing the drug dose	Withhold offending medication
Chemotherapy toxicity (eg, fluorouracil, capecitabine, methotrexate, ifosfamide, cytarabine, tacrolimus, cyclosporine)	Encephalopathy, seizures, and ataxia may occur rapidly or subacutely after cumulative dosing (especially in the setting of organ dysfunction or older patients)	MRI is often normal or nonspecific	Stabilization after withholding the offending agent	Varies, usually supportive (for ifosfamide toxicity, IV methylene blue)
Pituitary insufficiency or apoplexy	Hyponatremia, hypotension, diabetes insipidus	Can occur with direct tumor invasion, postradiation, or immunotherapy	Endocrine evaluation	Hormone supplementation, fluid restriction
Creutzfeldt-Jakob disease	Characteristic cortical and subcortical MRI changes	Rapid time course can be similar to paraneoplastic disorders	Real-time quaking-induced conversion assay Elevated 14-3-3 protein in CSF can be found in 12.5% of patients with paraneoplastic syndromes	Supportive care
Gluten ataxia	Gastrointestinal symptoms	Can co-occur with glutamic acid decarboxylase 65 (GAD65)–associated syndromes	Antigliadin/antitransglutaminase antibodies	Gluten-free diet
Genetic mitochondrial syndromes or glucose transporter type 1 deficiency[20,21]	Exercise or stress induced, stuttering course, seizures and movement disorder, family history of similar disorders, developmental delay	Mainly in children and adults <50 years old	High CSF lactate with mitochondrial disorders Low CSF glucose with glucose transporter deficiency MR spectroscopy Confirmatory genetic testing	Varies

CSF = cerebrospinal fluid; CT = computed tomography; DNA = deoxyribonucleic acid; EEG = electroencephalogram; IM = intramuscular; IV = intravenous; MRI = magnetic resonance imaging.

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CASE 7-1

A 75-year-old man who was a prior smoker presented with 2 months of weight loss. He had associated fatigue and loss of appetite and reported muscle pain and twitching with any activity, especially in his bilateral proximal lower limbs. He also reported light-headedness on sitting up or standing. On examination, he had marked orthostatic hypotension (FIGURE 7-1), myokymia especially in his forearm and distal leg muscles after activity or palpation, and prominent muscle atrophy. Serum testing confirmed the presence of anti–contactin-associated proteinlike 2 (CASPR2) antibodies. He had undergone prior CT screening for lung cancer which revealed a small left apical lung nodule not meeting guidelines for intervention due to size and stability on observation. Due to the anti-CASPR2 antibody, he was evaluated with positron emission tomography (PET) which revealed hypermetabolism of the lung nodule (FIGURE 7-1), the biopsy of which confirmed small cell lung cancer. He underwent stereotactic radiosurgery with concurrent corticosteroids and experienced gradual improvement in his symptoms, although ongoing mild fatigue, myokymia, and activity-induced myalgias continued.

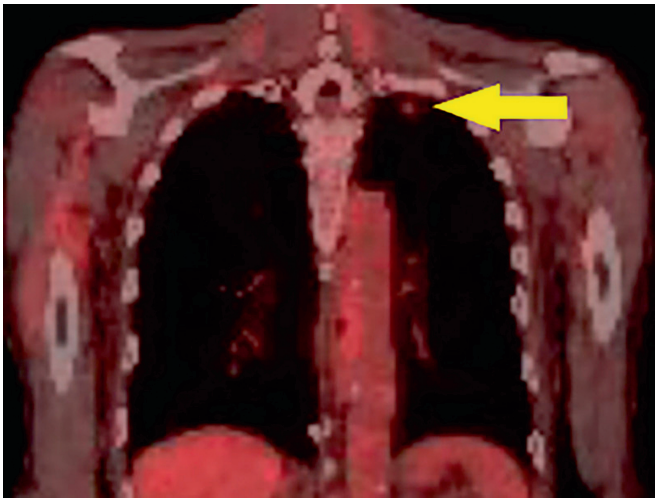

FIGURE 7-1
Imaging for the patient in CASE 7-1. Fludeoxyglucose positron emission tomography (FDG-PET) CT scan showing hypermetabolic left apical lung nodule (*arrow*), which biopsy confirmed as small cell lung cancer.

COMMENT

This case exemplifies common clinical features of anti-CASPR2 antibody syndromes, including fatigue, weight loss, myalgias, and myokymia, especially autonomic symptoms, and the importance of repeat imaging evaluation for occult malignancy.

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psychiatric symptoms, with 40% experiencing visual or auditory hallucinations, 25% developing acute schizoaffective disorder, 12% experiencing suicidal thoughts, and 6% attempting suicide.[26] One-half of patients have neurologic symptoms at presentation, and one-half also have hyperthermia, muscle rigidity, or rhabdomyolysis suggesting neuroleptic intolerance, which can cloud the diagnosis but distinguish this antibody from other limbic syndromes.[25] Insomnia and sleep inversions are common early symptoms in anti-NMDA-receptor encephalitis, with parasomnias, sleeptalking, and dream enactment occurring in more than 20% of patients.[9] Insomnia and sleep disturbances can be quite refractory in these patients and may persist after an otherwise good response to immunotherapy. Seventy percent of patients have seizures, often bilateral, with status epilepticus occurring in one-third of patients. Associated extreme "delta-brush" sign on EEG with rhythmic chewing is found in 30% of those with seizures, with autonomic seizure symptoms being rare compared with other antibody syndromes.[27,28] Seizures in this disorder and the extreme delta-brush sign are correlated with worse disease severity and outcomes, warranting earlier and more aggressive interventions.[27] However, at 2 years after diagnosis more than 90% of patients do not require ongoing antiseizure therapy.[25] More than 75% of patients will develop movement disorders, most often orofacial or lingual dyskinesias, but a wide spectrum of movement symptoms have been reported.[25] It is common for patients with anti-NMDA-receptor encephalitis to require intensive care unit stays for seizures, central hypoventilation, and dysautonomia, and significant cardiac dysautonomia can occur with bradyarrhythmia requiring pacing, as well as cardiac arrest; in one review, 7% of patients with anti-NMDA-receptor encephalitis had a significant cardiac event.[25] Urgent tumor removal and immunotherapy are very effective in this disorder in improving short-term and long-term outcomes, and if these are not effective within 4 weeks, there are studies supporting moving to second-line therapies with rituximab or cyclophosphamide to improve further recovery.[25]

It is now apparent that HSV encephalitis (and other infections, including COVID-19) may be a trigger for subsequent anti-NMDA-receptor encephalitis, occurring within 4 months in one-quarter of patients with HSV encephalitis in one prospective study, with the development of anti-NMDA-receptor or other antibodies preceding clinical anti-NMDA-receptor encephalitis, raising the question of whether proactive screening should be undertaken for patients with HSV encephalitis.[29]

Twelve percent of patients with anti-NMDA-receptor encephalitis have relapses within the next 2 years, often milder than their initial presentation, requiring repeat immunotherapy and raising the question of when or whether maintenance immune suppression is indicated. Up to 5% of patients may develop subsequent demyelinating diseases with anti–aquaporin-4 or anti–myelin oligodendrocyte glycoprotein (MOG) antibodies, and occasionally anti–glial fibrillary acidic protein (GFAP) antibodies as well.[25]

ANNA1 (Hu)-Associated Encephalitis

Antineuronal nuclear antibody type 1 (ANNA1) (Hu) antibody was one of the first characterized paraneoplastic antibodies, and has an extremely high association with underlying cancer, most commonly small cell lung cancer, with a preponderance in women.[30] Importantly, only a minority of patients will have a detectable tumor at the time of neurologic symptoms, but more than

KEY POINTS

- **Psychiatric and sleep disturbances, including suicidal thoughts or attempts, are common in anti–*N*-methyl-D-aspartate (NMDA)-receptor encephalitis.**
- **Up to 25% of patients with herpes simplex virus encephalitis may develop autoimmune encephalitis (mostly anti-NMDA-receptor) within 4 months, with antibodies preceding clinical onset.**

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three-quarters will be found to have cancer within 6 to 24 months from the time of first neurologic symptoms, serving as a reminder of the importance of repeated oncologic screening in patients with this paraneoplastic syndrome. The most common clinical syndrome is limbic encephalitis with a sensory neuronopathy which is found in more than two-thirds of patients, often causing significant sensory ataxia, but brainstem and cerebellar syndromes can also occur. Autonomic symptoms are found in one-quarter of patients. Response to oncologic treatment or immunotherapy is generally disappointing, with about one-half of patients stabilizing and very few noticeably improving, and the median survival time is approximately 7 months, highlighting the limits of immunotherapy in some paraneoplastic neurologic syndromes. Multiple reports have described the emergence of neurologic syndromes with ANNA1 (Hu) antibodies after immune checkpoint inhibitor therapy.[31]

AMPA-Associated Encephalitis

Antibodies against the glutamate A1 or A2 components of the AMPA receptor result in prominent amnesia with altered consciousness in 80% of patients, and two-thirds of patients will have an underlying tumor (40% have a thymoma, but lung, breast, and ovarian cancers occur as well). Insomnia is reported in 10% of patients with these antibodies. MRI demonstrates nonspecific fluid-attenuated inversion recovery (FLAIR) hyperintensities in three-quarters of patients, mostly in the temporal and insular regions, and one-half of patients will have an elevated CSF white blood cell concentration. Clinically, this syndrome can overlap with features of anti-NMDA-receptor encephalitis but other findings specific to anti-NMDA-receptor encephalitis have not been reported. Most patients with AMPA-associated encephalitis experience at least partial improvement with tumor-directed treatment and immunotherapy, but only 30% of patients have been reported to return to their prior baseline.[32]

Ma1-Associated and Ma2-Associated Encephalitis

Temporal lobe epilepsy with psychiatric changes is very common in anti-Ma antibody disorders, and seizures can be refractory. Testicular germ cell tumors are found in a high percentage of patients, and ultrasound can be more beneficial than standard CT in detecting occult tumors. Sleep disturbances are common in anti-Ma antibody disorders, with hypersomnia occurring in one-third of patients, and new-onset narcolepsy with cataplexy with decreased CSF hypocretin levels is a clue to these syndromes.[9,33] Sleep and psychiatric disturbances often persist even after appropriate treatment.[9,10]

LGI1-Associated Encephalitis

Three-quarters of patients with LGI1-associated encephalitis have seizures, which are more often focal than bilateral, including faciobrachial dystonic seizures (which seem to be unique among antibody-associated epilepsies) and pilomotor seizures that may localize to the right temporal lobe, in keeping with the autonomic symptoms sometimes associated with this disorder.[28,34] One study found that 30% of patients with epilepsy with confirmed ictal autonomic symptoms (eg, GI symptoms, piloerection, ictal fever, bladder dysfunction, cough) had anti-LGI1 antibodies.[35] Insomnia is especially common in this disorder, and parasomnia with dream enactment (confirmed by absence of atonia during rapid eye movement [REM] sleep on polysomnography) occurs in

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up to one-half of patients concurrent with symptom onset and often improves after immunotherapy.[9]

CASPR2-Associated Encephalitis

Morvan syndrome with peripheral nerve hyperexcitability is mainly associated with anti-CASPR2 antibodies but can also occur with anti-LGI1 antibodies. Cognitive and encephalitic symptoms occur as well but tend to be less overt. Insomnia is also common in Morvan syndrome, as are parasomnia with dream enactment, REM sleep without atonia, and very disturbed sleep architecture on polysomnography.[9,10]

GAD65-Associated Encephalitis

While more often associated with stiff person syndrome, GAD65 can also cause limbic encephalitis with refractory seizures.[36] Cognitive and encephalopathy symptoms are often much milder compared with other paraneoplastic encephalitic syndromes, possibly due to the focal nature of this disorder. Déjà vu or epigastric auras are characteristic of GAD65 syndromes compared with other antibody-associated seizures, matching the focal pathology, and are less common in other antibody-mediated epilepsies.[28] In addition, automatisms and impaired consciousness are common compared with other epileptogenic antibodies, while myoclonic features seem rare.[28]

GFAP-Associated Encephalitis

Antibodies against GFAP can be associated with a nonspecific clinical presentation or can occur in the setting of a characteristic clinical syndrome with unique imaging features: gradually progressive tremor, anxiety, ataxia, and myoclonus with diffuse leptomeningeal enhancement and distinctive radial vascular enhancement throughout the brain, brainstem, and spinal cord (FIGURE 7-2).[37] This disorder responds very well to immune suppression, often with corticosteroids alone, and one-third of patients will have an underlying tumor.[37]

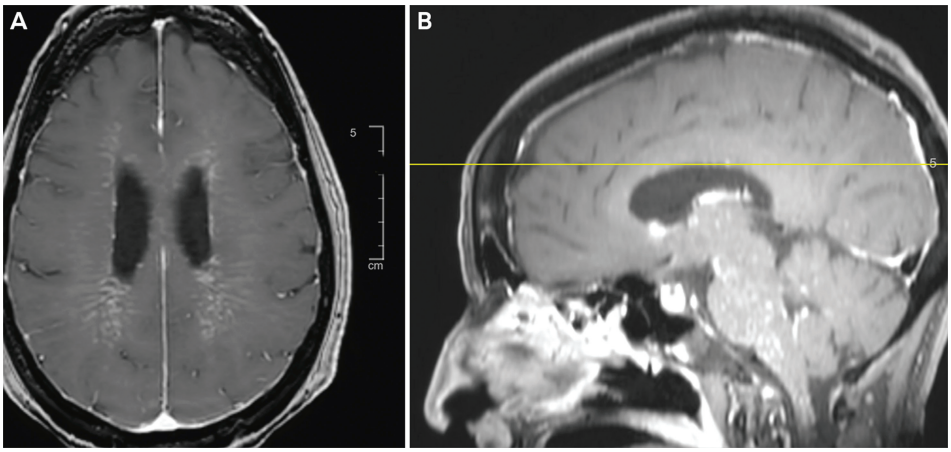

FIGURE 7-2

Axial (*A*) and sagittal (*B*) T1-weighted MRI with contrast showing diffuse radial vascular and leptomeningeal enhancement (*A*) and brainstem enhancement (*B*), which had near complete resolution after administration of corticosteroids. These imaging features are characteristic of glial fibrillary acidic protein (GFAP) astrocytopathy.

KEY POINTS

- **Focal faciobrachial dystonic or pilomotor seizures are a suggestive feature of anti–leucine-rich glioma inactivated protein 1 antibody–associated syndromes.**
- **Automatisms and impaired consciousness are much more common in glutamic acid decarboxylase 65 (GAD65)-associated epilepsy compared with other autoimmune epilepsies.**
- **Persistent neuropsychiatric symptoms are common after treatment of autoimmune encephalitis and require ongoing symptomatic support.**

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Cognitive Outcomes Following Paraneoplastic Encephalitis

A 2022 meta-analysis of the literature on neuropsychological assessments across several types of autoimmune encephalitis confirmed the significant neuropsychological symptom burden that persists even after improvements from therapy but also highlighted the dearth of systematic studies in the literature across the different types (notably ANNA1 [Hu]). Interestingly,

TABLE 7-4 **Paraneoplastic Limbic Encephalitis Syndromes**

Antibody	Clinical clues	Seizure frequency and symptomatology	MRI	Associated tumors	Treatment in addition to tumor removal
***N*-methyl-D-aspartate (NMDA)**	Psychosis, repetitive chewing, hypoventilation, catatonia	60% bilateral, status epilepticus in 1/3, "delta brush" on EEG in 1/3, ictal autonomic symptoms	Mostly normal or nonspecific fluid-attenuated inversion recovery (FLAIR) changes	15% to 40% teratoma (60% in women 18 to 45 years old)	Corticosteroids, plasma exchange, intravenous immunoglobulin (IVIg), rituximab, cyclophosphamide
Antineuronal nuclear antibody type 1 (Hu)	Sensory neuronopathy	2/3 EEG background slowing 40% epileptiform discharges	50% nonenhancing temporal FLAIR changes	Small cell lung cancer	
α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)	80% have amnestic syndromes with altered consciousness		Three-quarters abnormal but nonspecific	Two-thirds with cancer (thymoma, lung, breast, ovarian)	Corticosteroids, plasma exchange, IVIg, rituximab, cyclophosphamide
Ma1/Ma2	Narcolepsy or cataplexy, rapid eye movement sleep behavior disorders, hypothalamic dysfunction		Bilateral thalamic FLAIR hyperintensities	Testicular	Corticosteroids, plasma exchange, IVIg, rituximab, cyclophosphamide
Leucine-rich glioma inactivated protein 1	Daydreaming, dream enactment, parasomnias	75% faciobrachial dystonic, focal, pilomotor, status epilepticus is rare, ictal piloerection common	Mostly normal or nonspecific anterior temporal FLAIR hyperintensities	<5% thymoma, lung, breast	Corticosteroids, plasma exchange, IVIg, rituximab
Glutamic acid decarboxylase 65 (GAD65)	Prior or concurrent diabetes, stiff person syndrome, or cerebellar symptoms	65% déjà vu auras, bilateral, ictal piloerection, rare status epilepticus	Focal hippocampus changes	<5% thymoma	Corticosteroids, plasma exchange, IVIg, rituximab
Glial fibrillary acidic protein (GFAP)	Anxiety, tremors, slow progression		Radial vascular and leptomeningeal enhancement	1/3, various tumors	Corticosteroids

EEG = electroencephalogram; MRI = magnetic resonance imaging.

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several studies report that persistent apathy posttreatment was very common (TABLE 7-4) (CASE 7-2).[38]

MOVEMENT DISORDERS

Symptoms of movement disorders can occur in many paraneoplastic disorders but are rarely the sole or dominant manifestation of a paraneoplastic disorder. Some paraneoplastic encephalitides can have concurrent basal ganglia and sleep dysfunction and may be confused with dementia with Lewy bodies, where fludeoxyglucose positron emission tomography (FDG-PET) or dopamine

CASE 7-2

A 50-year-old woman had a new-onset witnessed seizure preceded by several days of vague episodes of confusion. Postictally, she had a normal examination, but brain MRI showed diffuse left lateral and mesial temporal fluid-attenuated inversion recovery (FLAIR) hyperintensities with mild mass effect without enhancement. CSF testing was normal and the infectious workup was negative. Serum and CSF were positive for anti–α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antibodies and CT found an enlarged right axillary lymph node, the biopsy of which confirmed metastatic breast carcinoma (estrogen receptor–positive, progesterone receptor–positive, *HER2*-negative). Mammogram was normal but breast MRI showed abnormal enhancement without discrete mass. A positron emission tomography (PET) scan was negative.

She was started on levetiracetam, but 6 weeks later had rapidly worsening confusion and memory loss over a week without overt seizures. She was treated with plasma exchange with slight improvement and then had one dose of rituximab with cyclophosphamide with stabilization of mental status but residual aphasia and short-term memory loss. The nonspecific right-breast enhancement was then biopsied confirming invasive ductal carcinoma, and she underwent radical mastectomy followed by chemotherapy for breast cancer with doxorubicin, cyclophosphamide, and docetaxel, followed by breast radiation and prophylactic contralateral mastectomy with maintenance letrozole hormonal therapy. Fifteen months after her initial diagnosis, repeat brain MRI showed significant left temporal atrophy with leukoencephalopathy. Five years after her initial diagnosis, she had gradual slight improvement but with residual moderate significant memory loss and fluent aphasia with exaggerated startle responses (eg, her dog barking, doors slamming, lights being turned on). Her spouse reported that she continued to need constant supervision due to her memory issues, but her attention and concentration were noticeably improved, and she had benefited from a daily routine using written plans and reminders. He also felt that her mood and anxiety had noticeably improved after starting a selective serotonin reuptake inhibitor (SSRI) 2 years prior.

COMMENT

This case describes the typical clinical presentation and long-term clinical and imaging sequelae of anti-AMPA-receptor encephalitis.

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single-photon emission computed tomography (SPECT) may again be useful. Parkinsonism can be seen in association with antineuronal nuclear antibody type 2 (ANNA2) (Ri), anti-Ma2, and anti–dipeptidyl-peptidase–like protein 6 antibodies, and choreas and dystonia can be seen in the setting of ANNA1 (Hu), CASPR2, collapsin response mediator protein-5 (CRMP-5, also known as CV2), and LGI1 syndromes.[39] More than 75% of people with GFAP astrocytopathy have concurrent movement symptoms, most often ataxia, tremor, or myoclonus, and rarely opsoclonus or ocular flutter.[40] Creutzfeldt-Jakob disease typically presents with similar features to paraneoplastic syndromes and can have overlapping clinical symptoms, especially with LGI1 syndromes.[41] In addition, glucose transporter type 1 deficiency commonly has episodic attacks with seizures and movement symptoms (eg, chorea).[20]

OPHTHALMIC SYNDROMES

Cancer-associated retinopathy is one of the more common paraneoplastic syndromes, and progress has been made in identifying underlying antibody associations (eg, enolase, recoverin, transient receptor potential cation channel subfamily M member 1). Thorough ophthalmic evaluation can be very helpful in characterizing these syndromes as well as clues to various mimics. The rapidly expanding armamentarium of oncology treatments contains many medications that can cause ophthalmic disorders (eg, immunotherapies, mitogen-activated kinase and many other tyrosine kinase inhibitors, antiangiogenic agents), so a thorough history of timing in relation to oncologic treatment is essential. Enolase antibody-associated retinopathy tends to occur years after an original cancer diagnosis and is associated with pure cone dysfunction.[42] Melanoma-associated retinopathy has particular features including male predominance, specific bipolar cell dysfunction with sparing of photoreceptors on electroretinogram resulting in central vision loss, and impaired night vision months to years before melanoma diagnosis, and mandates a thorough search for an occult melanoma.[43] Most melanoma-associated retinopathy cases do not have an identifiable antibody association, but anti–transient receptor potential cation channel subfamily M member 1 antibodies have been found in a subset of patients.[43] Confident diagnosis in melanoma patients during oncologic treatment can be especially challenging when antibody tests are negative, given that immunotherapy and mitogen-activated protein kinase inhibitors are common treatments and can cause retinopathies as well. Bilateral diffuse melanocytic proliferation is a rare disorder highly associated with underlying cancers, characterized by progressive painless bilateral vision loss with cataracts and retinal detachment with bacillary layer detachment on optical coherence tomography. IgG antibodies that induce melanocyte proliferation have been described, supporting the use of plasma exchange in these patients.[44]

Optic Neuropathy

Optic neuropathy from occult leptomeningeal metastases, systemic vascular disease, or oncologic medications (eg, antiangiogenic, immunotherapy, platins) is far more common than paraneoplastic optic neuropathy. However, progressive painless unilateral or bilateral vision loss can certainly occur as an isolated paraneoplastic syndrome or together with other disorders (eg, in association with recoverin, ANNA1 [Hu], GAD65, LGI1, NMDA, or GFAP antibodies). Optic neuropathy together with subacute dementia, ataxia, or

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neuropathy should prompt consideration of a CRMP-5–associated syndrome which is frequently associated with underlying lung or other tumors.[45] Neuromyelitis optica spectrum disorders (NMOSDs) with anti–aquaporin-4 antibodies are much more common than paraneoplastic optic neuropathies, and can be associated with underlying tumors in approximately 5% of cases; paraneoplastic cases are more likely in men more than 50 years old presenting with intractable nausea and vomiting, with underlying lung or breast adenocarcinomas.[46] Associated tumors seem to be more rare with anti-MOG antibodies, although they can co-occur with anti-NMDA-receptor antibodies.[47]

KEY POINT

● Anti–aquaporin-4 antibodies are associated with cancer in 5% of cases, especially in men more than 50 years old with intractable vomiting.

Opsoclonus-Myoclonus Syndrome

In children, opsoclonus-myoclonus syndrome can occur as part of parainfectious or other autoimmune disorders but is also associated with underlying neuroblastoma or other tumors in one-half of cases. Opsoclonus or ocular flutter in adults can be part of ANNA1 (Hu) or ANNA2 (Ri) syndromes, especially if other features of these disorders are present, and about one-half of adults will have an underlying tumor.[48]

Ocular Clues to Other Paraneoplastic Syndromes

Ocular findings on examination can be clues to other paraneoplastic syndromes, including downbeat nystagmus with ganglion layer thinning on optical coherence tomography in stiff person syndrome with high-titer anti-GAD65 antibodies.[49] Anti–nicotinic acetylcholine receptor antibodies can cause pupillary dysfunction with hippus and light sensitivity in addition to autonomic, GI, and bladder dysfunction.

BRAINSTEM SYNDROMES

Several paraneoplastic syndromes can exhibit prominent brainstem symptoms, especially those associated with ANNA1 (Hu), anti-Ma2, anti–Kelchlike protein 11, ANNA2 (Ri), anti–dipeptidyl-peptidase–like protein 6, and anti–leucine zipper 4 antibodies (TABLE 7-5), but they are usually accompanied by other manifestations.

IgLON5-Associated Syndromes

IgLON5-associated disorders are unique in that they often exhibit isolated brainstem symptoms and a very high incidence of sleep disturbances with breathing disorders, with more than one-half of patients having sleep apnea, often with stridor (which should be screened for and treated), dream enactment, poor non-REM architecture, and sleep fragmentation with REM sleep without atonia.[9,10]

For patients with brainstem syndromes and area postrema symptoms (ie, intractable hiccups, nausea and vomiting, or involvement around the medulla oblongata) anti–aquaporin-4 or anti-GFAP antibody associations should be considered (see Optic Neuropathy section).[50]

Isolated cochleovestibulopathy has rarely been reported as a paraneoplastic syndrome related to a variety of tumors, but no characteristic tumor or antibody has been described.[51]

CEREBELLAR SYNDROMES

Anti–PCA-1 (Yo) antibodies remain the most commonly recognized association with paraneoplastic cerebellar syndromes and predominantly occur in women

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with underlying breast or ovarian cancers (tumor risk is 90% with these syndromes). It is suspected that anti–PCA-1 (Yo) antibodies respond to the cerebellar degeneration related protein 2 like antigen in Purkinje cells, and the use of this specific antigen in diagnostic testing increases specificity to reduce false positives (positive PCA-1 [Yo] results in men are usually false positive).[52] GAD65 antigens are common in patients with type I diabetes and at low levels are nonspecific, but when they are present in high titers (>2000 U/mL) they are more likely to be associated with clinical neurological autoimmunity. In a 2015 study, gluten sensitivity was shown to co-occur with anti-GAD65 antibodies in

TABLE 7-5 **Paraneoplastic Brainstem Syndromes**

Antibodies	Clinical Clues	Tumor associations	Treatment
Purkinje cell cytoplasmic antibody type 1 (Yo/cerebellar degeneration related protein 2 like)	Brainstem, cranial nerve, or peripheral neuropathies; 8% hyperacute strokelike syndromes	90% breast (often *HER2*+), ovarian carcinoma	Tumor directed
Antineuronal nuclear antibody type 1 (Hu)	Limbic encephalitis, sensory neuronopathy	>90% (small cell lung cancer)	Tumor directed and immunotherapy (generally poor response)
Kelch-like protein 11	Brainstem signs, limbic encephalitis, myeloneuropathy, 25% hyperacute onset, 25% tinnitus or hearing loss	80% testicular seminoma	One-half of patients will stabilize or improve with immunotherapy and cancer treatment
Ma1/Ma2	MRI changes in superior colliculi and periaqueductal gray	>90% testicular cancers	One-third of patients improve with tumor removal or treatment and immunotherapy
IgLON family member 5	Bulbar symptoms, sleep disturbance, cognitive impairment, slower progression over months	10%, various types	Varies
Antineuronal nuclear antibody type 2 (Ri)	90% have extracerebellar symptoms: opsoclonus-myoclonus syndrome, spasticity, brainstem signs, parkinsonism, jaw opening dystonia, slower multistep progression over months	70% breast, lung carcinoma	Tumor removal, corticosteroids, plasma exchange, intravenous immunoglobulin, rituximab
Dipeptidyl-peptidase–like protein 6	Progressive encephalomyelitis with rigidity and myoclonus, encephalitis	10% hematologic malignancies	Varies
Neurochondrin	Chorea, brainstem, myelopathy	10%, various types	Varies
Glutamate ionotropic receptor kainate type subunit 2	Hydrocephalus, encephalitis, myoclonus	25% Hodgkin lymphoma, teratoma	Varies
Leucine zipper protein 4	Polyradiculopathy and lower motor neuron symptoms, encephalitis	Germ cell seminomas	Tumor removal and immunotherapy

MRI = magnetic resonance imaging.

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up to 70% of patients with anti-gliadin antibodies, anti-transglutaminase antibodies, or both.[53] In addition, prior, concurrent, or subsequent temporal lobe epilepsy or stiff person syndrome symptoms occur in approximately 30% of patients with high-titer anti-GAD65 antibodies and cerebellar syndromes.[36]

It is estimated that up to 20% of patients with cerebellar ataxia who have an otherwise negative workup may have an autoimmune syndrome and lack a confirmatory diagnostic test, but the characteristic development of subacutely progressive gait ataxia (ie, developing over weeks, reaching a nadir at 6 months, with initially normal MRI but developing midline vermian atrophy) is very typical of all of these syndromes, and initial cerebellar hypermetabolism on PET followed by later hypometabolism has been reported.[11,54] Downbeat nystagmus (especially vibration-induced nystagmus) is a recently described manifestation that appears more often in paraneoplastic cerebellar syndromes compared with nonparaneoplastic syndromes.[11,55] When atrophy is already present on initial imaging, a nonimmune cause is much more likely (eg, toxic, genetic, metabolic) (TABLE 7-6) (CASE 7-3).

KEY POINTS

- Patients with anti–glutamic acid decarboxylase 65 (GAD65) antibodies can have varying associated syndromes (eg, epilepsy, cerebellar syndromes, diabetes) over their lifetimes.
- Downbeat nystagmus (especially when vibration-induced) is suggestive of a paraneoplastic cause of cerebellar ataxia.

MYELOPATHIC SYNDROMES

Myelitis can be seen as part of numerous paraneoplastic syndromes affecting other parts of the nervous system (eg, ANNA1 [Hu], aquaporin-4, MOG, GFAP, CRMP-5, amphiphysin, ANNA2 [Ri], PCA-1 [Yo], and GAD65 syndromes), but pure myelitis as a manifestation of paraneoplastic syndromes is rarer and 20% of these patients will not have any identifiable antibody.[56] It is important to remember that several more common causes of nonparaneoplastic myelopathy can be occult on standard imaging (eg, leptomeningeal metastases, compressive lesions only revealed by dynamic imaging with weight loading or flexion and extension).[57] Atypical infectious causes of myelitis can also mimic paraneoplastic disorders in immunosuppressed patients (eg, varicella-zoster virus, HSV).[57] In patients with longitudinally extensive transverse myelitis, aquaporin-4–associated syndromes should be considered (see Optic Neuropathy section). For those with partial myelitis, multiple sclerosis, MOG or aquaporin-4, or sarcoid (especially if posterior leptomeningeal enhancement or the "trident" sign is present) should be considered. Diffuse spinal leptomeningeal enhancement should prompt consideration of GFAP astrocytopathy (see Limbic Encephalitis section).[58] Paraneoplastic myelitis usually has linear T2-weighted hyperintensity on sagittal images and can have snake-eyes changes on axial MRI, with punctate symmetric T2-weighted hyperintensity in the bilateral anterior horns, although these features can be seen in other toxic or ischemic myelopathies as well.

STIFF PERSON SYNDROME

Stiff person syndrome presents with spasms, rigidity, and hyperlordosis with simultaneous activation of agonist and antagonist muscles due to antibody effects on inhibitory interneurons. Typically affecting the proximal limbs and trunk and resulting in gait dysfunction, this syndrome is usually associated with high-titer anti-GAD65 antibodies and a less than 5% incidence of associated tumors.[49] Rarer phenotypes include progressive encephalomyelitis with rigidity and myoclonus with anti–glycine receptor antibodies, and more distal limb presentations with anti-amphiphysin antibodies (which have a much higher incidence of associated cancers) and other rarer antibodies (eg, dipeptidyl-peptidase–like protein 6, Zic4, GABA receptor-associated protein,

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γ-aminobutyric acid A [$GABA_A$] receptor).[49] Other common symptoms in stiff person spectrum disorders include anxiety, excessive startle responses and hyperekplexia (especially with anti–glycine receptor antibodies), seizures and focal hippocampal sclerosis, vestibulo-ocular symptoms with downbeat nystagmus, and cerebellar ataxia and tremor, and 25% to 50% of patients have upper or lower GI dysmotility or both.[36,49] Physical therapy combined with long-acting benzodiazepines and other muscle relaxers (eg, baclofen, tizanidine) and focal botulinum therapy can provide tremendous symptomatic relief, but refractory cases or those with prominent functional burden should be considered for immunotherapies (eg, corticosteroids, intravenous immunoglobulin [IVIg], plasma exchange, rituximab, mycophenolate, cyclophosphamide, methotrexate, stem cell transplant). Neurogenic dysphagia in these patients is also common and underappreciated.[59] Patients with stiff person spectrum disorders have a higher incidence of diabetes, so screening for hyperglycemia is important (especially when administering corticosteroids or glucose-containing IVIg) (CASE 7-4).[36,49]

TABLE 7-6 **Cerebellar Paraneoplastic Syndromes**

Antibodies	Clinical clues	Tumor association	Treatment
Purkinje cell cytoplasmic antibody type 1 (Yo/cerebellar degeneration related protein 2 like)	Brainstem, cranial nerve, or peripheral neuropathies; 8% hyperacute strokelike	90% breast (often *HER2*+), ovarian carcinoma	Tumor directed
Purkinje cell cytoplasmic antibody type 2/microtubule associated protein 1B	Sensorimotor neuropathy, encephalomyelitis	80% lung, breast carcinoma	Tumor directed
SRY-box transcription factor 1	Lambert-Eaton myasthenic syndrome	90% small cell lung cancer	Most patients improve with tumor removal or treatment and corticosteroids, intravenous immunoglobulin (IVIg), plasma exchange, rituximab
Tr-delta/notch-like epidermal growth factor–related	Optic neuritis, encephalopathy, sensory neuropathy	90% Hodgkin lymphoma	Varies
Kelch-like protein 11	Brainstem signs, limbic encephalitis, myeloneuropathy, 25% hyperacute, 25% tinnitus or hearing loss	80% testicular seminoma	Tumor removal or treatment and corticosteroids, IVIg, plasma exchange, cyclophosphamide
Metabotropic glutamate receptor 1	Cognitive or behavioral symptoms	10%, generally hematologic malignancies	Corticosteroids, plasma exchange
IgLON family member 5	Bulbar symptoms, sleep disturbance, cognitive, slower progression over months	10%, various malignancies	Varies

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PERIPHERAL NERVE SYNDROMES

Peripheral neuropathies may be one of the most challenging manifestations of paraneoplastic syndromes, given the much more common toxic (chemotherapy, radiation) and compressive or infiltrative peripheral neuropathies that can occur in patients with cancer, as well as the common peripheral neuropathies that often occur in the general population. In particular, checkpoint inhibitors and other immunotherapies can cause atypical neuropathies including acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and mononeuritis multiplex. Careful localization and confirmatory imaging and electrodiagnosis can be very useful in assessing for occult compressive and infiltrative causes. Compressive neuropathies are especially common in patients with rapid weight loss or decreased mobility, particularly ulnar neuropathy at the elbow and fibular neuropathy at the knee. A careful history regarding alcohol use should always be elicited in these patients who are often under extreme nutritional and psychological stress. Given the intense immune suppression in many of these

CONTINUED FROM PAGE 1796

Antibodies	Clinical clues	Tumor association	Treatment
Contactin-associated proteinlike 2	Limbic encephalitis, Morvan syndrome; may start with episodic paroxysmal ataxia	Varies (higher when Morvan syndrome is present)	Corticosteroids, plasma exchange, IVIg, rituximab
Antineuronal nuclear antibody type 2 (Ri)	90% have extracerebellar symptoms: opsoclonus-myoclonus syndrome, spasticity, brainstem signs, parkinsonism, jaw opening dystonia, slower multistep progression over months	70% breast, lung carcinoma	Tumor removal, corticosteroids, plasma exchange, IVIg, rituximab
Glutamic acid decarboxylase 65 (GAD65)	Chronic progression over months, overlap with limbic encephalitis, temporal lobe epilepsy, or stiff person syndrome in ~30%		Concurrent antigliadin/ antitransglutaminase antibodies in 70%
Dipeptidyl-peptidase–like protein 6	Progressive encephalomyelitis with rigidity and myoclonus, encephalitis	10% hematologic malignancies	Varies
Neuronal intermediate filament light chain	Encephalomyeloradiculopathy	50% neuroendocrine tumors	
Inositol 1,4,5-trisphosphate receptor type 1	Myelopathy, sensory neuropathy	30% breast or other malignancies	
Rho GTPase activating protein 26	Cognitive dysfunction, hyperekplexia	50%, various malignancies	
Neurochondrin	Chorea, brainstem syndromes, myelopathy	10%, various malignancies	
Glutamate ionotropic receptor kainate type subunit 2	Hydrocephalus, encephalitis, myoclonus	25% Hodgkin lymphoma, teratoma	
Seizure related 6 homolog like 2	Parkinsonism	20% ovarian carcinoma	

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patients, investigating and treating occult atypical causes of infection (eg, varicella-zoster virus, HSV) is crucial.

Subacute sensory neuronopathy with asymmetric patterns and notable pain is the most common paraneoplastic peripheral neuropathy (associated with ANNA1 [Hu]), but virtually any pattern can occur including mononeuritis multiplex, sensorimotor (associated with CRMP-5/CV2, antineuronal nuclear antibody type 3, and anti–Purkinje cell cytoplasmic antibody type 2) and acute motor neuropathies, autonomic neuropathies (associated with ANNA1 [Hu] and anti–Purkinje cell cytoplasmic antibody type 2), and peripheral nerve hyperexcitability (in Morvan syndrome associated with anti-CASPR2, anti-LGI1, or anti-Netrin1 antibodies).[60] More recently, anti–Kelch like protein 11 antibodies (which can also cause brainstem or cerebellar syndromes) have been described as associated with testicular seminoma and causing a myeloneuropathy syndrome. Nonspecific antibodies like neurofilament light chain and SRY-box transcription factor 1 can be found associated with peripheral and cranial neuropathies in patients with cancer, but they can also be found at elevated levels in patients with small cell lung cancer without neurologic symptoms.

CASE 7-3

A 66-year-old man had a subacute onset of diffuse four-limb ataxia and tremor with gait imbalance, dysarthria, intractable nausea with hiccups, diplopia, and downbeat nystagmus over 3 weeks. Initial brain MRI was normal but a paraneoplastic syndrome was suspected, and body CT revealed multiple retroperitoneal masses and enlarged lymph nodes, the biopsy of which led to the diagnosis of retroperitoneal stage IV metastatic Merkel cell carcinoma. CSF cytology was negative and serum and CSF paraneoplastic panels were negative. He was treated with corticosteroids, intravenous immunoglobulin (IVIg), cisplatin, and etoposide and had shrinkage of his tumors. His cerebellar symptoms did not improve but stopped worsening, and after chemotherapy he experienced a slight improvement and was able to ambulate with a walker. Two months later, follow-up brain MRI showed bilateral superior cerebellar fluid-attenuated inversion recovery (FLAIR) hyperintensities without enhancement and corresponding hypermetabolism on positron emission tomography (PET). He was treated with pembrolizumab checkpoint inhibitor immunotherapy without neurologic changes. Five months later he developed new hemiparesis; MRI showed diffuse brain and spine metastases, and he died soon afterward.

COMMENT

This case highlights a typical paraneoplastic cerebellar syndrome and the importance of repeat imaging, since initial imaging can be normal and cerebellar changes are often subtle or appear months later. Paraneoplastic panels do not always find a diagnostic antibody, and this case exemplifies the uncertainties of oncologic immunotherapies in patients with paraneoplastic syndromes. New symptoms require reassessment since leptomeningeal and CNS metastases can still occur.

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Since both monoclonal gammopathies and peripheral neuropathies are increasingly common with age (prevalence of approximately 1% each in the sixth decade, and up to 10% each in the ninth decade), establishing a causal relationship can be challenging. Patients with monoclonal gammopathies can have a variety of peripheral neuropathy patterns; in particular, IgM monoclonal gammopathies of undetermined significance (MGUS) can cause demyelinating patterns that may respond to immunotherapy, while IgG and IgA tend to have less frequent associations with axonal neuropathies. All patients with MGUS should undergo hematologic evaluation because of the association with progression to Waldenström macroglobulinemia (which is sometimes associated with anti–myelin-associated glycoprotein [MAG]-antibody neuropathy, causing painful sensory loss in the legs and sensory ataxia) and multiple myeloma, which can cause lambda amyloidosis neuropathies (especially carpal tunnel syndrome and painful diffuse sensorimotor neuropathies). In addition, these cancers can cause neurolymphomatosis or Bing-Neel syndrome, so CSF cytology, flow cytometry, MRI with contrast, and PET should be considered, as well as nerve biopsy if necessary.[61] Neurophysiologic testing can be extremely helpful in distinguishing paraproteinemic demyelinating neuropathies from other neuropathies, showing prolonged distal motor latencies without conduction block, and a terminal latency index (distal nerve conduction distance/[proximal motor conduction velocity × distal motor latency]) of less than 0.25.[61] Treatment consists of corticosteroids, cyclophosphamide, or rituximab (375 mg/m^2 IV weekly for 4 weeks) and usually produces at least some improvement, especially if started earlier in the symptom course.[61] It should be remembered that patients with monoclonal gammopathies (especially IgM with very high protein levels) can also have abrupt neurologic symptoms due to hyperviscosity syndromes with acute stroke, headache, retinal hemorrhages, deafness, delirium, and ataxia that responds to plasma exchange.[61]

Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) is a rare paraneoplastic syndrome with diffuse skin and organ edema and rapidly progressive neuropathy with similarities to chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) symptoms and is caused by an underlying solitary plasmacytoma. Patients may become quadriparetic within weeks. Bone or CT scans usually identify the plasmacytoma, and surgical resection or radiation can induce recovery. Occult endocrinopathies should be screened for to prevent adrenal collapse and other potentially fatal complications. Diffuse vascular leakage is caused by circulating vascular endothelial growth factor (VEGF), which is elevated in the serum in the majority of patients. In a 2022 study, chemotherapy with dexamethsone, the proteasome inhibitor ixazomib, and the VEGF inhibitor lenalidomide also showed clinical imrpovements in small series.[62] TABLE 7-7 summarizes the paraneoplastic peripheral neuropathies.

MYASTHENIC SYNDROMES

Lambert-Eaton myasthenic syndrome is characterized by acute or subacute progressive symmetric proximal limb weakness that may improve with repeat activation, as can be confirmed by the electrodiagnostic finding of facilitation or incremental response after brief exercise. Autonomic dysfunction is common and symptoms are often initially mistaken for generalized fatigue. anti–P/Q-type

KEY POINTS

- Diabetes is common in patients with stiff person syndrome, so patients should have appropriate screening, especially before using corticosteroids or high-glucose immunoglobulin therapy.
- Up to 20% of patients with immune checkpoint inhibitor–associated myasthenia gravis may have concurrent myositis and myocarditis.

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voltage-gated calcium channel antibodies are confirmatory and Anti–SRY-box transcription factor 1 antibodies can be found as well, but a minority of patients will have other rare or no identifiable antibody.[6] The presence of weight loss, current smoking, or age over 50 years each increases the risk of an underlying tumor,[63] and cancer screening is recommended and should be repeated if necessary. Resection or other treatment of the underlying tumor often provides substantial relief, as can steroids, IVIg, and plasma exchange. The potassium channel blocker amifampridine can provide symptomatic relief if residual symptoms remain, and there are reports of benefit from anti–CD19-blocking or anti–CD20-blocking antibodies.[64]

Myasthenia gravis with anti–acetylcholine-receptor antibodies has a 10% to 15% association with occult thymoma (although up to 70% of patients have focal thymic germinal center hyperplasia), and thymectomy has now been shown in a randomized controlled trial to help achieve symptom control in nonthymomatous patients.[65] Thymoma association and the benefit of thymectomy are less established in anti–muscle-specific kinase (MuSK) antibody myasthenia (in which rituximab appears to be more beneficial), as

CASE 7-4

A 51-year-old woman presented for gradually worsening back pain with muscle spasms over the last 6 months, which recently began affecting her balance and causing falls. She had hyperlordosis with increased muscle tone in truncal muscles and rigidity of both proximal legs. Serum and CSF were positive for anti–glycine receptor antibodies. Screening for underlying tumors was negative. Over the next 6 years, she was treated with clonazepam, baclofen, and tizanidine, as well as physical therapy, corticosteroids, intravenous immunoglobulin (IVIg), plasma exchange, focal botulinum toxin, and rituximab. She experienced partial improvement in pain but gradually worsening stiffness and spasms with gait imbalance, requiring a quad walker to ambulate. She had a prominent startle response, with light and sound changes inducing painful spasms. She then developed worsening right hemiparesis with increased floaters in her right eye. MRI showed a diffusion-restricting left basal ganglia mass and vitreous sampling revealed vitreoretinal (ocular) lymphoma (FIGURE 7-3). While undergoing treatment with high-dose methotrexate, she had rapid and dramatic improvement in her symptoms, such that she was able to ambulate independently and reduce the dosages of her antispasmodics. After five doses of methotrexate, she achieved complete remission from her lymphoma and underwent an autologous stem cell transplant for lymphoma consolidation. Six months later, she continued to require physical therapy, tizanidine, and focal botulinum only and had sustained improvement in her symptoms.

COMMENT

This case describes a typical clinical evaluation, the somewhat atypical and more refractory features of anti–glycine receptor antibody stiff person syndrome, and the necessity of long-term consideration of associated malignancies.

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well as late-onset syndromes and older patients.[66] Occasionally, rapid-onset refractory myasthenia is the presenting symptom of a malignant thymoma.

The widespread use of immune checkpoint inhibitors has introduced a new myasthenia syndrome, primarily seen in older men within 8 weeks of treatment. The majority of these patients have anti–acetylcholine receptor antibodies (although anti-titin, anti-Kv1.4, and other antibodies have been reported), which can produce severe bulbar and respiratory symptoms in one-quarter of patients with significant mortality. These agents are also associated with frank necrotizing myositis with elevated creatinine kinase and even myocarditis, which should be considered and screened for in these patients.[66] Of the many newly studied treatments for myasthenia gravis, it is not yet clear which are most beneficial for immune checkpoint inhibitor–associated myasthenia gravis, but a substantial number of cases are severe and refractory.

AUTOIMMUNE AUTONOMIC GANGLIONOPATHY

Autoimmune autonomic ganglionopathy associated with neuronal ganglionic α3 or β4 acetylcholine receptor is worthy of special attention. These antibodies

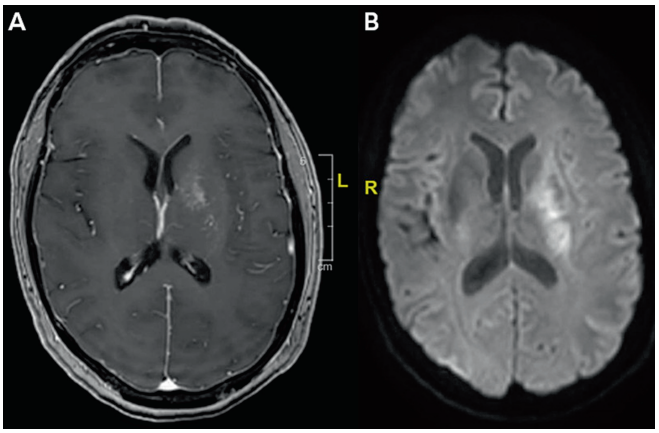

FIGURE 7-3

Imaging of the patient in CASE 7-4. Axial T1-weighted postcontrast MRI showing infiltrative enhancement (*A*) with diffusion restriction (*B*) in the left basal ganglia of a patient with 6 years of stiff person syndrome and anti–glycine receptor antibodies refractory to antispasmodic and immunomodulatory therapies with new-onset hemiparesis. Recent bilateral floaters and vitreous sampling led to a diagnosis of vitreoretinal (ocular) lymphoma. The patient's long-standing refractory symptoms improved dramatically with high-dose methotrexate, to the point that she could ambulate without an assistive device for the first time in more than 5 years.

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cause internalization of the receptor by cross-linking and interrupt neuronal mediation of autonomic adrenergic, sudomotor, or cardiovagal (especially with anti-β4 antibodies) signaling; however, false positives and false negatives can occur in 30% to 40% of patients so clinical syndromes and alternate diagnoses must be considered carefully.[67] Three-quarters of patients present subacutely, but 25% are acute and 14% of patients recall a viral prodromal illness. Three-quarters of patients will have orthostatic hypotension and constipation, often of abrupt onset and moderate to severe in nature, and one-half will have sicca symptoms, anhidrosis, and autonomic bladder dysfunction. One-third of patients will have sexual dysfunction or upper GI dysmotility (eg, achalasia, esophageal dysphagia, gastroparesis). Twenty percent of patients will have cardiac arrhythmias and 10% will have pupillary dysfunction (detectable by hippus light reactions with fluctuating pupillary size despite constant light exposure). One-third of patients will have sensory

TABLE 7-7 **Paraneoplastic Peripheral Neuropathies**

Syndrome	Clinical clues	Antibodies	Tumors	Mimics	Treatment
Subacute sensory neuronopathy (relatively specific for paraneoplastic mechanism)	Asymmetric, pain, dorsal root and posterior column symptoms (sensory ataxia)	Antineuronal nuclear antibody type 1 (ANNA1) (Hu), antiglial nuclear antibody (AGNA), SRY-box transcription factor 1, amphiphysin	Small cell lung cancer	Cerebellar ataxia, neuropathy, vestibular areflexia syndrome, anti-Abs against Argonaute, anti-fibroblast growth factor receptor 3	Tumor directed, pain control
Sensorimotor neuropathy (nonspecific)	Asymmetric	Antineuronal nuclear antibody type 3; collapsin response mediator protein-5; Purkinje cell cytoplasmic antibody type 2 (PCA-2); inositol 1,4,5-trisphosphate receptor type 1; AGNA; myelin-associated glycoprotein	Lung, myeloma, thymoma	Similar to many other sensorimotor neuropathies	Tumor removal or treatment, intravenous immunoglobulin (IVIg), plasma exchange, rituximab
Polyradiculopathy		Amphiphysin, leucine zipper 4 (LZUP4)		Immune checkpoint inhibitors (eg, nivolumab), neurolymphomatosis	Varies
Motor neuropathy (rare)		LZUP4	Germ cell tumors, lymphoma	Brentuximab, ado-trastuzumab, larotrectinib, underlying mild Charcot-Marie-Tooth disease exacerbated by chemotherapy	Varies

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symptoms or cognitive and psychiatric changes, and 15% will have endocrine dysfunction with hyponatremia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and amenorrhea. Concurrent autoimmune disorders are common in one-third of patients (eg, Sjögren syndrome, sarcoidosis, autoimmune thyroid disease) and 11% will have an underlying tumor (eg, ovarian, lung, GI). In addition, chronic Chagas disease may elicit a similar syndrome due to molecular mimicry and muscarinic or adrenergic antibodies.[68] Detailed autonomic testing, including bladder and cardiac function testing or esophageal and GI motility studies, can be very helpful in confirming the autonomic dysfunction and assessing for alternate causes. Treatment with corticosteroids, IVIg, or plasma exchange produces significant improvement in the majority of patients but may need repeated treatments or tapering to prevent relapses in some cases, and pyridostigmine has been reported to be of symptomatic benefit.

CONTINUED FROM PAGE 1802

Syndrome	Clinical clues	Antibodies	Tumors	Mimics	Treatment
Neuromyotonia	Myokymia	Contactin-associated proteinlike 2 (CASPR2), leucine-rich glioma inactivated protein 1, netrin 1	Lung, thymoma		Steroids, IVIg, and plasma exchange are usually beneficial
Autonomic neuropathy		ANNA1 (Hu), PCA-2, CASPR2	Lung, thymoma	Various chemotherapies, diabetes	Varies
Cryoglobulinemia	Acral distribution, temperature sensitive	IgM (high levels)	Hematologic malignancies	Vasculitis	Tumor directed, plasma exchange, rituximab
Myeloneuropathy	Bladder symptoms, combined hyporeflexia and hyperreflexia, pain	Kelchlike protein 11	Testicular seminoma	Vitamin B_{12} or copper deficiencies, human T-cell lymphotropic virus	Tumor directed

IgM = immunoglobulin M.

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MUSCLE SYNDROMES

Dermatomyositis and polymyositis have a prevalence of 8 out of 100,000 people, with two peaks between ages 5 and 15 years and 40 and 60 years with female predominance. One-half of patients with dermatomyositis have typical skin changes preceding myopathic symptoms including heliotrope rash (upper eyelid and "shawl" distribution) and Gottron's erythematous papules in a linear pattern on the extremities, especially the dorsal and lateral aspects of the hands and fingers but also overlying joints. Within 2 years of onset, 3% to 15% of patients with dermatomyositis will be found to have an underlying malignancy (eg, GI, ovarian, nasopharynx, breast), and the risk may be higher in patients with amyopathic disease, dysphagia, rapid progression, recurrence of symptoms on steroid taper, and high creatine kinase levels, and in male patients and those between 15 and 50 years old.[69] "Honeycomb" edema on MRI of the quadriceps muscles has also been associated with an 85% increased risk of malignancy.[70] A variety of antibodies have been described in dermatomyositis, and anti–nuclear matrix protein 2, anti–melanoma differentiation-associated protein 5, and anti–transcription intermediary factor-γ antibodies have been associated with an increased risk of underlying malignancy. Notably, anti–transcription intermediary factor-γ antibodies in those under 40 years old appear to imply no increased risk of malignancy, but the same antibody in a patient over 50 years old implies a higher risk of associated malignancy.[71] Seronegative necrotizing autoimmune myopathy may also be associated with occult malignancy.

Whole-body MRI has been studied to help diagnose and fully characterize the extent of the various paraneoplastic myopathic syndromes prior to biopsy and serologic test results and may have the added benefit of simultaneously screening for underlying tumors and signs of associated collagen vascular diseases and avascular necrosis, which are common in these patients.[72]

TREATMENT PRINCIPLES

The treatment of paraneoplastic disorders generally involves a combination of treating the underlying malignancy and immunomodulation. Paraneoplastic neurologic syndromes have a high burden of morbidity, mortality, and cost due to the complexity of their diagnosis and the frequent need for prolonged inpatient care including intensive care unit stays, testing, and treatment (many of which can be challenging to negotiate with insurers), as well as prolonged supportive multidisciplinary care for residual disability after diagnosis and treatment.[73] Improved and more efficient diagnostics and effective therapies to reduce disability are an urgent priority. Many cancer multidisciplinary teams are accustomed to following evidence-based guidelines, especially regarding indications for surgical resections, which do not consider paraneoplastic disorders. For example, most patients with focal breast cancers would undergo neoadjuvant chemotherapy prior to resection, but in the presence of a paraneoplastic disorder, tumor removal is paramount, so surgical oncologists must be willing to deviate from their usual practice. Also, patients with paraneoplastic neurologic syndromes can be extremely impaired, and many oncology teams are accustomed to applying functional scales (eg, Karnofsky, Eastern Cooperative Oncology Group, World Health Organization) to determine which patients are likely to benefit from treatment.[74] In these scales, most patients who are mobility limited (which is true of many patients with paraneoplastic neurologic disorders) would not qualify, so patients may need an

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advocate to surpass these barriers that evidence-based medicine and health care systems unintentionally impose. Cooperation and communication among the multidisciplinary neurologic and oncologic team is crucial in these situations.

ANTIBODY-NEGATIVE PARANEOPLASTIC NEUROLOGIC SYNDROMES

Perhaps the most challenging situation is one where a paraneoplastic neurologic disorder is suspected but a confirmatory antibody or cancer is not found. Unfortunately, this is common and the treating team must make difficult decisions about how far to pursue alternate diagnoses, as well as more invasive oncologic and neurologic testing (including nervous system biopsies) and immunosuppressive therapies with increasing side effects and risks. A careful review of family and social history, repeating detailed systemic examinations for findings suggestive of other disorders, and remembering the comparative rarity of some of the possible diagnoses are crucial in these cases. Input from experts across different disciplines (especially infectious diseases, genetics, and radiology) can be very helpful, and a "team leader" should be established to keep clear and open communication with the patient and family about the diagnostic uncertainties and steps taken.

KEY POINT

- **In patients with dermatomyositis, amyopathic or male patients, those with rapid progression, dysphagia, high creatine kinase levels, antibodies against nuclear matrix protein 2, melanoma differentiation-associated protein 5, or transcription intermediary factor-γ, or "honeycomb" MRI changes in the quadriceps muscles are associated with increased risk of malignancy.**

CONCLUSION

Incredible progress has been made in the last decade in diagnosing and treating paraneoplastic neurologic syndromes, but more work is needed to improve long-term symptomatic outcomes. Numerous challenges remain, such as whether patients with paraneoplastic neurologic disorders can safely receive potentially life-saving cancer immunotherapies, and to ensure that recent advances are applied equitably across patient populations.

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Neurologic Complications of Conventional Chemotherapy and Radiation Therapy

By Jennie W. Taylor, MD, MPH

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **Neurologic complications are among the most common and feared outcomes of cancer treatments. This review discusses the signs and symptoms, mechanisms, and management of the most common peripheral and central neurologic complications of chemotherapy, radiation therapy, and antiangiogenic therapy during cancer treatment and in survivors.**

LATEST DEVELOPMENTS: **The landscape of cancer treatments is evolving to include more targeted and biologic therapies, in addition to more traditional cytotoxic therapies and radiation therapy. With increasingly complex regimens and longer survival for patients with cancer, the early recognition and management of neurologic complications is key to improving the morbidity and mortality of patients living with cancer.**

ESSENTIAL POINTS: **Neurologists should be familiar with acute central and peripheral toxicities that can occur during cancer treatment and delayed toxicities that can occur years after exposure. Neurologists should be familiar with the clinical and radiologic presentations of these complications and strategies for management.**

INTRODUCTION

Neurologic complications are common among many cancer treatments. They range from acute central and peripheral toxicities during treatment to delayed toxicities that can occur years after exposure. These complications are often difficult to distinguish from cancer recurrence and thorough neurologic assessment is often needed. As the landscape of cancer treatments grows beyond cytotoxic therapies and radiation therapy to targeted therapies, biologics, and immunotherapies, neurologists will be increasingly called upon to manage these patients alongside their oncology and radiation oncology colleagues. For more on immunotherapies in cancer treatment, see the article "Neurologic Complications of Cancer Immunotherapy," by Nancy Wang, MD,[1] in this issue of *Continuum*.

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An important reference for neurologists to be aware of is the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), a grading system on a 5-point scale that standardizes adverse events for patients with cancer.[1] The CTCAE includes a section on nervous system disorders and, although an important part of clinical trial research, it has become increasingly used to guide treatment decisions for oncologists and can serve as a common ground between treating clinicians for managing toxicity related to treatment.

Below is a grading scale of cancer treatment adverse events, modified from the CTCAE[1]:

- **Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.**
- **Grade 2: moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).**
- **Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- **Grade 4: life-threatening consequences; urgent intervention indicated.**
- **Grade 5: death related to adverse events.**

This article reviews the most common neurologic complications of chemotherapy and radiation therapy.

NEUROLOGIC COMPLICATIONS OF CHEMOTHERAPY

Conventional chemotherapeutic agents have long been recognized to cause central and peripheral nervous system toxicities. These complications are a frequent source of neurologic consultation, and neurologists should be familiar with these entities.

Acute Central Toxicities

Several cancer-directed therapies may result in acute central neurologic toxicities. The most common manifestation is an acute encephalopathy, and cerebellar ataxia and aseptic meningitis are seen in association with a limited number of agents (TABLE 8-1[2]).[3] Acute encephalopathy often occurs within hours to days of exposure and presents with a constellation of confusion, seizures, and altered mental status. Underlying mechanisms vary depending on the offending agent but are generally related to the cytotoxic effects on endothelial and neuroglial cells.[3] Risk factors include the dose of cytotoxic agent, method of delivery (IV versus intrathecal), prior radiation exposure, and patient comorbidities such as renal or hepatic impairment and prior neurologic injury. MRI is often unremarkable or nonspecific and symptoms are often self-limiting.

High doses of cytarabine are associated with an acute cerebellar disorder in up to 25% of patients, with risk factors including an age of 40 years or older, a dose of 30 grams or more, and abnormal liver or renal function.[4] Ataxia is usually seen within 5 days of treatment, often preceded by encephalopathy, and should result in immediate discontinuation of the drug. Although often self-limiting, permanent deficits have been reported, and the mechanism presumptively involves Purkinje cell injury.[4]

Aseptic meningitis can develop after treatment with intrathecal cytotoxic medications such as methotrexate and cytarabine.[5] Acute onset of symptoms

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often occurs within hours of injection and may last up to 3 days. The symptoms may include headaches, nuchal rigidity, nausea and vomiting, fever, and altered mental status. CSF examination demonstrates elevated protein with pleocytosis and negative cultures. A short course of steroids may be needed, but symptoms are usually self-limiting.

Leukoencephalopathy

Leukoencephalopathy is a severe, delayed complication from cytotoxic agents such as methotrexate. The diagnosis is supported by the observation of extensive white matter hyperintensity on T2-weighted MRI and often brain atrophy. While some patients may be asymptomatic, most experience progressive cognitive decline or dementia with an onset of months to years after exposure.[5] The risk is dose dependent (either IV or intrathecal) and significantly elevated when combined with radiation therapy and intrathecal treatment in patients with untreated hydrocephalus.[5] Although the mechanism of action is not definitively understood, preclinical work suggests potentiation of methotrexate-induced toxicity when combined with radiation, and myelination deficits from microglia activation.[6] The decision to continue treatment can be complex and must be balanced between symptomatic burden and response to therapy.

Peripheral Neurotoxicity and Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common toxicities of cancer therapy. Acutely, it may limit the delivery of effective treatment and is an important survivorship issue that may significantly impact morbidity, particularly in breast and colon cancer survivors, where platinum-based therapy is the backbone of treatment. The highest rates of occurrence are in patients treated with cisplatin and oxaliplatin, taxanes (paclitaxel), vinca alkaloids, and proteasome inhibitors such as bortezomib (TABLE 8-2[2]). Oxaliplatin can induce an acute neurotoxicity that manifests as cold sensitivity, throat discomfort, muscle cramps, and perioral numbness. These symptoms often occur within hours to days of the first two doses and improve quickly, although some patients with severe symptoms may not have complete resolution. Paclitaxel is similarly associated with an acute painful neuropathy. Although the overall incidence varies, it has been estimated to occur in up to 68% of patients after treatment with this agent.[7]

The development of CIPN is mostly dose dependent and increases with higher cumulative single-dose administration, and also with combination therapy. The risk of CIPN is higher in patients with metabolic syndrome, obesity, and diabetes. At the patient level, risk factors include poorly controlled diabetes, an age of 75 years or older, preexisting neuropathy, and Charcot-Marie-Tooth disease (CMT) type 1A.[8] Vincristine may cause a severe neuropathy in patients with CMT type 1A which may resemble Guillain-Barré syndrome and this agent should be avoided in these patients. In general, the experience of CIPN can be highly variable for each patient.

Although the natural history of CIPN varies and recovery is often incomplete, the majority of cases occur within the first 2 months of treatment, progress while on active therapy, and gradually improve after treatment is discontinued. In contrast, patients exposed to platinum therapy (ie, cisplatin and oxaliplatin) may experience *coasting*, which is a worsening of symptoms for approximately

KEY POINTS

- The Common Terminology Criteria for Adverse Events is a widely accepted grading system for assessing adverse events caused by cancer treatments. Neurologists should be familiar with the grading system for neurologic complications when coordinating care for patients with cancer.
- Acute central neurologic toxicities associated with chemotherapy require heightened awareness for early detection and management to minimize neurologic morbidity.
- Acute central neurologic toxicities are seen more commonly with high doses of cytotoxic agents, prior radiation exposure, intrathecal administration, and comorbid renal and hepatic dysfunction.
- Vincristine may cause a severe neuropathy in patients with Charcot-Marie-Tooth disease type 1A which may resemble Guillain-Barré syndrome and this agent should be avoided in these patients.
- Chemotherapy-induced peripheral neuropathy occurs most frequently within the first 2 months of treatment and is usually dose dependent, and early recognition is key as treatment dose and frequency adjustments can minimize the impact on cancer survivors.

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3 months after treatment is stopped. For other agents, most notably paclitaxel, only one-half of patients significantly recover 6 months later, with high rates of persistent symptoms lasting for years.[9-11]

Symptoms are usually dose-dependent and manifest as a painful sensory axonal neuropathy in a stocking-and-glove distribution. A motor neuropathy is associated with paclitaxel and thalidomide in 14% and 40% of patients, respectively, and vincristine may induce an autonomic neuropathy and sensory neuronopathy at high doses.[11]

Guidelines for the consensus prevention and management of CIPN and extensive literature reviews have been published by the American Society of Clinical Oncology jointly with the European Society for Medical Oncology, European Oncology Nursing Society, and European Association of Neuro-Oncology.[8,12]

TABLE 8-1 **Common Acute Central Nervous System Chemotherapy Toxicities**[a]

Acute encephalopathy

- 5-Fluorouracil
- Antiangiogenics
- Carmustine (BCNU)
- Cisplatin
- Cyclophosphamide
- Cytosine arabinoside
- Doxorubicin
- Etoposide
- Fludarabine
- Ifosfamide
- Interferons
- Interleukin 1 and 2
- Methotrexate
- Procarbazine
- Tamoxifen
- Thalidomide
- Thiotepa
- Vincristine

Cerebellar toxicity

- High-dose cytarabine

Aseptic meningitis

- Intrathecal methotrexate
- Intrathecal cytarabine

Data from Dietrich J, Continuum (Minneap Minn).[2]

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Evaluation using neurophysiologic examinations may be helpful (TABLE 8-2[2]), although they are not recommended for symptom monitoring during treatment and may be discordant with a patient's symptoms.

MANAGEMENT. The early recognition of symptoms and necessary adjustments to medication dosage and frequency are key to minimizing the impact of CIPN on patients with cancer. No preventative measures have been shown to demonstrate efficacy in large phase 3 trials, although early evidence is encouraging for cryotherapy with frozen socks and gloves (level of evidence II, grade of recommendation C),[13] exercise and functional training (level of evidence II, grade of recommendation C),[14] and compression therapy (level of evidence III, grade of recommendation C).[15] Vitamin D deficiency may be a risk factor for developing CIPN in patients receiving paclitaxel and therefore should be repleted if low.[16]

If CIPN symptoms remain mild, it is recommended to continue treating with a full dose of chemotherapy. However, if symptoms increase significantly and impact function, the risk of disabling neurotoxicity increases and must be weighed against continuing treatment. If CIPN worsens during active treatment, it is important to discuss a dose reduction, delay, or discontinuation, alternative treatment schedules, or less neurotoxic alternatives. Treatment delays or dose reduction can improve symptoms in certain cases, such as with the use of taxanes and bortezomib. Published guidelines on dose reductions for specific agents such as platinum-based treatments are available.[11]

Characteristics of Chemotherapy-induced Peripheral Neuropathy[a] TABLE 8-2

Pattern	Symptoms	Examination findings	Chemotherapies	Electrodiagnostic findings
Large fiber sensory-predominant neuropathy	Pain and paresthesia, allodynia, hyperalgesia, imbalance, numbness of hands and feet	Stocking-and-glove pattern, impaired light touch, vibration, and proprioception, positive Romberg sign	Platinum derivatives, taxanes, thalidomide	Low amplitude sensory nerve action potential amplitudes and slowed velocities
Small fiber neuropathy	Painful, burning sensation	Stocking-and-glove pattern, impaired pin-prick and temperature sensation	Vinca alkaloids, taxanes, thalidomide, and bortezomib	May be normal, but skin biopsy can confirm small C and Aδ fiber degeneration
Motor neuropathy	Weakness, tremor, cramps	Decreased reflexes, distal weakness, atrophy	Paclitaxel and thalidomide	Low amplitude compound muscle action potentials and slowed velocities
Autonomic neuropathy	Constipation, orthostasis, bladder dysfunction	Postural hypotension, reduced variability of heart rate	Vincristine and bortezomib	

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Several options can be considered for symptomatic treatment (TABLE 8-3). A large randomized trial showed that duloxetine 60 mg (starting at 30 mg and titrating up) reduces pain severity from 59% to 38%[17] in patients with CIPN and seems to have higher efficacy in platinum-based therapies (level of evidence I, grade of recommendation B), with lower levels of evidence for venlafaxine, tricyclic antidepressants, and antiseizure medications such as gabapentin and pregabalin (level of evidence V, grade of recommendation B), or opioids.[8] Topical approaches may also be beneficial and low risk with menthol cream (level of evidence III, grade of recommendation B), particularly for small fiber neuropathies.[8]

TABLE 8-3

Approaches to Treating Pain Associated With Chemotherapy-induced Peripheral Neuropathy[a]

Intervention	Evidence level, recommendation grade	Notes
Pharmacologic		
Duloxetine	I, B	More pronounced benefit with platinum-based regimens
Venlafaxine	II, C	
Amitriptyline	II, C	Consider if contraindication or failure from duloxetine
Nortriptyline	II, D	
Pregabalin	II, C	Consider if contraindication or failure from duloxetine
Gabapentin	II, D	
Tramadol	II, C	Recommended as palliative option
Opioids	II, C	
Topical interventions		
Menthol cream	III, B	Low dose (1%) concentration; recommended for small fiber neuropathy
Capsaicin	III, C	8% patches; most data supported from other causes of neuropathic pain
Nonpharmacologic		
Exercise and functional training	II, B	Early intervention is key and recommended at symptom onset and can be considered preventatively
Acupuncture	II, C	May be beneficial for treatment in select patients
Neurofeedback and guided cognitive behavioral therapy	II, C	Eg, Proactive Self-Management Program for Effects of Cancer Treatment

[a] Data from Jordan B, et al, Ann Oncol.[8]

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Given the possible chronic nature of CIPN and its potential for significant impacts on morbidity and quality of life, patients may benefit from working with physical and occupational therapists to minimize the risks of falls, increase mobility, and evaluate for assistive devices. Again, early intervention and education can be beneficial in adjusting patient and caregiver expectations.

Physical activity during chemotherapy treatments that carry a high risk of developing CIPN may prevent loss of strength, improve balance, slow down the development of symptoms, and stabilize function. Online cognitive and behavior-based pain management interventions, such as the Proactive Self-Management Program for Effects of Cancer Treatment (PROSPECT), are also under investigation.[18] A multimodal training program while undergoing treatment can improve postural stability and strength, decreasing the risk of falls and related injuries.[19]

Cerebrovascular Complications

Bevacizumab, its biosimilars, and other antiangiogenic therapies are broadly used across multiple malignancies. Although its use in patients with central nervous system (CNS) involvement (either from primary or metastatic disease) has prompted concerns for increased risk of CNS hemorrhage, several large safety analyses have not found higher risks of intracranial hemorrhage in patients with nonhemorrhagic lesions treated with bevacizumab, erlotinib, or sunitinib and sorafenib.[20,21] Antiangiogenic treatment may increase the risk of intracranial hemorrhage in patients on anticoagulation therapy, and decision making in these cases may be more complex.

Additional neurologic complications from antiangiogenic agents include cerebrovascular ischemia from arterial thromboembolic events and posterior reversible encephalopathy syndrome (PRES) which, despite its name, may not always be reversible and can occur anywhere in the brain. PRES manifests with headaches, mental status and visual changes, and seizures. Hypertension is often present and, in the context of cancer-directed therapy, is likely caused by antiangiogenic-induced hypertension.[22]

Cancer-Related Cognitive Impairment

One of the most concerning complications of chemotherapy treatment for cancer survivors is the development of cognitive deficits that linger beyond the course of treatment. Cognitive impairment can significantly impact survivors' quality of life and ability to return to work after treatment. The mechanism behind this phenomenon is complex, including altering the normal cognitive trajectory of aging,[23] inflammatory changes,[24] direct toxicity on neural progenitor cells, and disruption of structural brain networks.[25] The underlying disease state is also likely a contributor.

Neuropsychological testing often reveals memory impairment, slower processing speed, executive dysfunction, and impaired attention.[25] Imaging is frequently performed to evaluate for tumor recurrence in the CNS but is not imperative for assessment and may not correspond with the degree of deficits. Risk factors include lower cognitive reserve, undertreated comorbid psychological illnesses such as anxiety and depression, and fatigue. Additional factors already discussed, such as the agent, radiation exposure, the specifics of certain treatments, and underlying disease, are also risk factors.

Supportive treatment including optimizing sleep and encouraging regular exercise and a healthy diet are likely beneficial. Cognitive and behavioral

KEY POINTS

- Effective treatments for pain associated with chemotherapy-induced peripheral neuropathy include duloxetine, tricyclic antidepressants, antiseizure medications, and topical and nonpharmacologic approaches.
- Neurologists should be able to recognize the cerebrovascular complications of antiangiogenic therapy and radiation therapy to minimize morbidity and mortality from cancer treatment.
- Risk factors for developing cancer-related cognitive impairment include lower cognitive reserve, anxiety and depression, fatigue, exposure to radiation, and the specifics of certain treatments.

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rehabilitation strategies with licensed neuropsychologists, group therapy sessions, and digital programming are all options and are increasingly being offered through cancer centers. Pharmacologic options such as modafinil,[26] methylphenidate,[27] and donepezil[28] have demonstrated encouraging results in improving cognition in cancer survivors, although large randomized trial data are lacking.

Additional Neurologic Toxicities

Following the CTCAE grading system, adverse events of the nervous system and psychiatric disorders are commonly seen in several targeted agents that are increasingly being used in cancer therapy. These include symptoms ranging from dizziness and headaches to cognitive changes and memory impairment. Fortunately, these are often low grade and infrequently lead to treatment disruption. Patients and families should be counseled about the risk of developing these adverse events and encouraged to report symptoms for accurate monitoring.

NEUROLOGIC COMPLICATIONS OF RADIATION THERAPY

Radiation therapy continues to be a cornerstone of the management of neoplastic processes involving the brain and spinal cord. The ionizing effects of radiation therapy lead to double-stranded DNA breakage and cell death, using the therapeutic ratio to maximize damage to neoplastic cells while minimizing risk to surrounding healthy cells. It can be delivered in a fractionated manner, as cumulative small daily doses delivered over a broader area to minimize toxicity to normal tissue, or stereotactically with higher doses delivered to a smaller volume in a shorter period.

Improved survivorship among patients with cancer has increased attention on the impact of radiation on survivors, particularly as it relates to cognition. Although fractionated radiation therapy continues to be the mainstay for treating diffuse primary brain tumors (often over a 5-week to 6-week course, up to 54 Gy to 60 Gy), stereotactic approaches are increasingly being used instead of whole-brain radiation for managing metastatic disease. Proton radiation therapy can further increase precision and lower exposure to surrounding tissue due to its more rapid dose fall-off.[29] Although clearly beneficial in specific settings, such as treating pediatric tumors, its widespread use in adult cancer therapy targeting the CNS remains limited compared with photon-beam radiation therapy.

Neurologic complications of radiation therapy can be considered in three temporal phases with somewhat differing pathophysiologies, treatment approaches, and outcomes. Factors known to increase the risk of developing toxicity include larger treated volumes of normal brain and higher total radiation doses given over fewer fractions. Brain toxicity is seen more often in a bimodal distribution with younger (ie, ≤5 years old) and older patients being at higher risk. Certain concurrent or sequential chemotherapy combinations can also increase neurotoxicity.

Acute Neurotoxicity

Acute neurotoxicity occurs during the first 1 to 2 months after the completion of radiation therapy. Fatigue is the most common symptom of acute toxicity, often limiting daily activities and increasing daytime sleep. Fatigue often peaks at the end of radiation therapy, although it may start early in the course and last a few

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weeks after completion. Headaches are also common, but progressive headaches or those associated with neurologic deficits should be assessed for possible increased intracranial pressure as they may require treatment with glucocorticoids to reduce cerebral edema. Radiation fractions of 3 Gy or more are more likely to cause acute encephalopathy, manifesting as headache, somnolence, nausea, focal neurologic deficits, and fever; however, this is rarely seen given that most daily fractionations are now 3 Gy or less.[30] Although often temporary, treatment with glucocorticoids, bevacizumab, or even surgery may be needed to manage symptoms, especially if progression remains a high clinical suspicion.

Risk factors for developing this neurologic complication include the volume of brain treated, total dose, and fractionation. A larger volume and higher dose over a shorter fraction can increase the likelihood of developing acute toxicity. A bimodal age distribution occurs in acute radiation neurotoxicity, with patients 5 years old and younger and older patients being most affected.

Early-Delayed Phase

In the early-delayed phase up to 6 months after radiation, fatigue and focal neurologic symptoms may persist and are often related to edema. Pseudoprogression is often seen in this window and can occur in up to 30% of patients with high-grade cancers treated concurrently with intensity-modulated radiation therapy and temozolomide.[31–33] It can also be seen after concurrent treatment with immune checkpoint inhibitors and radiation therapy for brain metastases. This is a radiologic diagnosis characterized by increased enhancement and fluid-attenuated inversion recovery (FLAIR) hyperintensity within the high-dose radiation field and typically corresponds with worsening neurologic symptoms. The diagnosis is often confirmed retrospectively based on the clinical trajectory (CASE 8-1).

Delayed Phase

Late effects, which develop more than 6 months after completing radiation therapy, are slower to develop and not reversible. Radiation necrosis is a particularly difficult long-term complication of cranial irradiation. It is thought to be caused by vascular injury, which leads to fibrinoid necrosis of small vessels and parenchymal necrosis. It typically occurs at least 1 year after treatment but can occur up to a decade after exposure.[34] Similar to pseudoprogression, it can be difficult to distinguish from tumor progression when within the high-dose radiation field. Radiologic findings include a contrast-enhancing, centrally necrotic mass with significant surrounding edema. Advanced imaging features such as decreased cerebral blood volume on MRI, a high lipid peak on MR spectroscopy, and a lack of uptake of radiotracers on positron emission tomography (PET) are all suggestive of radiation necrosis, and can be helpful but are not sufficient for distinguishing radiation necrosis from tumor progression, and tissue confirmation may be required.[35] Treatment is similar to that of pseudoprogression, running the spectrum from active surveillance if a patient is asymptomatic to glucocorticoids, bevacizumab, or even resection if symptoms are severe. Bevacizumab is an approved treatment for radiation necrosis, and at low doses (5 mg/kg IV every 2 weeks or 7.5 mg/kg IV every 3 weeks for four doses) can improve symptoms and radiologic response.[36,37] Laser interstitial thermal therapy is an emerging treatment option for radiation necrosis, particularly in the management of brain metastases.[38]

KEY POINTS

- Factors that increase the risk of developing toxicity from radiation therapy include a larger volume of normal brain in the radiation field and a higher total radiation dose given over fewer fractions.
- Pseudoprogression is often seen within 6 months of radiation therapy, in the early-delayed phase, and can occur in up to 30% of high-grade cancers treated concurrently with intensity-modulated radiation therapy and temozolomide.
- Radiation necrosis is a long-term complication of radiation therapy that may occur several years after exposure and can resemble tumor recurrence. It may be effectively treated with bevacizumab.

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CASE 8-1

A 75-year-old right-handed man presented with transient right-sided weakness concerning for cerebral ischemia. Imaging revealed an enhancing lesion in the left frontal lobe (FIGURE 8-1A) with masslike fluid-attenuated inversion recovery (FLAIR) hyperintensity (FIGURE 8-1B). He underwent a subtotal lesional resection (FIGURE 8-1C and 8-1D) and pathology confirmed an *MGMT*-methylated glioblastoma. During the last week of his course of fractionated radiation and concurrent temozolomide, he developed increased right-sided weakness and seizures. Imaging revealed increased enhancement (FIGURE 8-1E) and FLAIR hyperintensity (FIGURE 8-1F). These findings were interpreted to reflect pseudoprogression and he was started on bevacizumab for symptom management, with a dramatic clinical response and improvement in both enhancement (FIGURE 8-1G) and FLAIR signal (FIGURE 8-1H). He went on to complete 12 cycles of adjuvant temozolomide and remained progression free for 2 years.

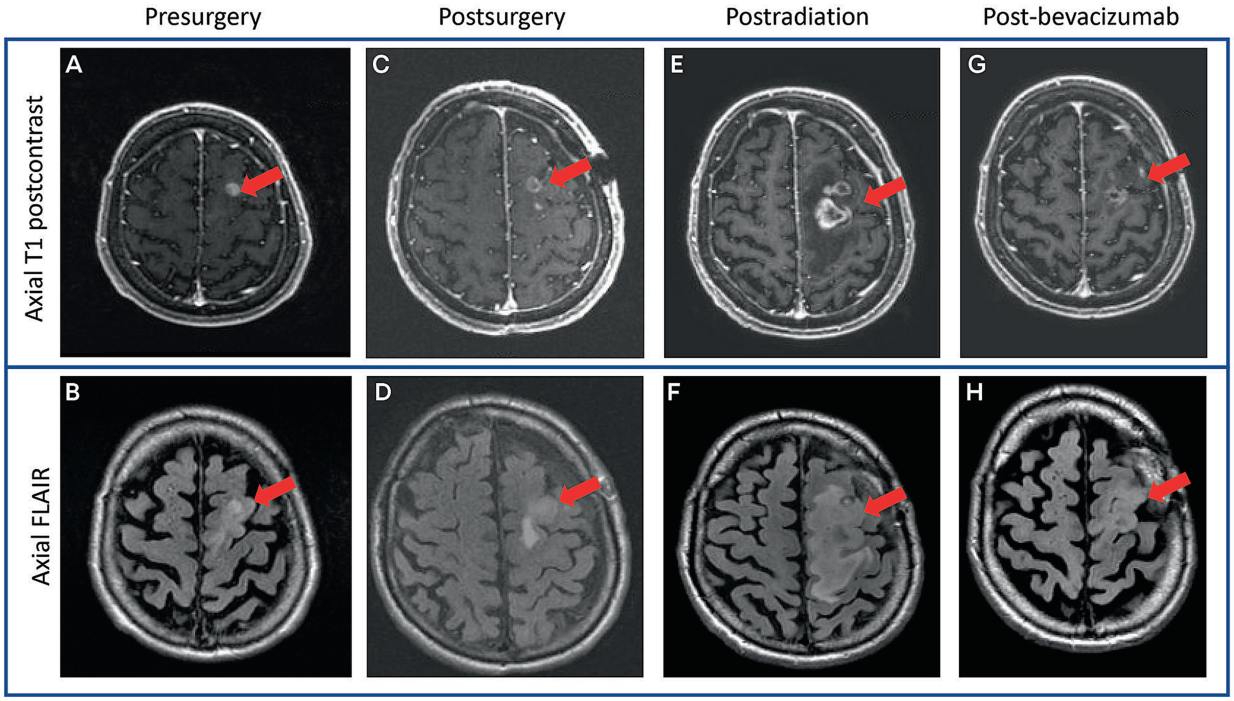

FIGURE 8-1

Imaging of the patient in CASE 8-1. Axial MRI sequences reveal a left frontal enhancing lesion (*A*) with masslike fluid-attenuated inversion recovery (FLAIR) hyperintensity (*B*). The patient underwent subtotal resection (*C*, *D*) and pathology confirmed a glioblastoma. After radiation therapy and concurrent temozolomide treatment, imaging reveals increased enhancement (*E*) and FLAIR signal (*F*) which correlates with increased right-sided weakness and is interpreted as consistent with pseudoprogression. An improvement in enhancement (*G*) and FLAIR hyperintensity (*H*) is seen after starting bevacizumab. *Arrows* highlight areas of abnormality.

COMMENT

This case describes the imaging pattern of pseudoprogression, a commonly seen early-delayed complication of radiation therapy that was successfully treated with antiangiogenic therapy.

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CASE 8-2

A 59-year-old left-handed woman with a history of hypertension presented with focal seizures manifesting as expressive aphasia and confusion. Imaging revealed a left frontal enhancing mass lesion that was confirmed to be glioblastoma. She received standard treatment with fractionated radiation therapy of 60 Gy with concurrent temozolomide, followed by 12 cycles of adjuvant temozolomide. Five and one-half years after diagnosis, she developed recurrent seizures, again manifesting as aphasia and confusion. Imaging revealed new restricted diffusion (FIGURE 8-2A) and speckled enhancement (FIGURE 8-2B). She was diagnosed with strokelike migraine attacks after radiation therapy (SMART) syndrome and was started on lacosamide. Her symptoms resolved and follow-up imaging confirmed the improvement of restricted diffusion (FIGURE 8-2C) and enhancement (FIGURE 8-2D).

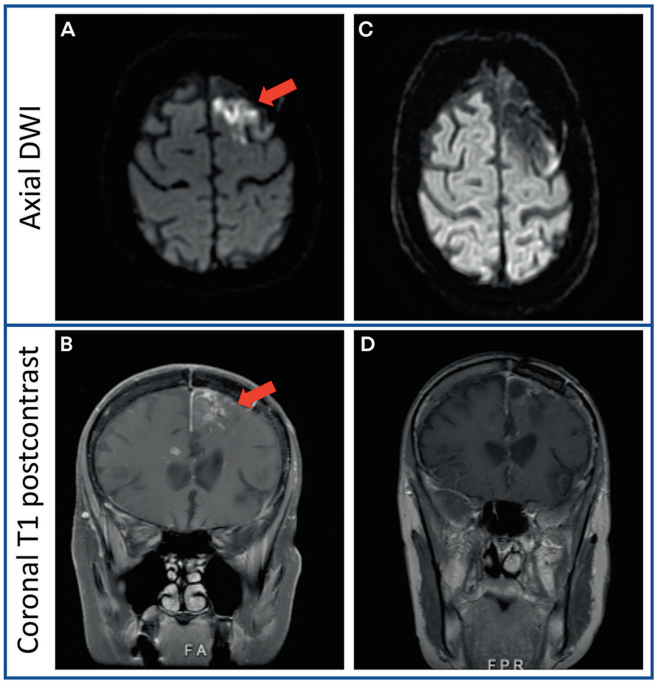

FIGURE 8-2
Imaging of the patient in CASE 8-2 shows MRI sequences suggestive of strokelike migraine attacks after radiation therapy (SMART) syndrome following radiation therapy and concurrent temozolomide treatment for left frontal glioblastoma. Axial diffusion-weighted imaging (DWI) reveals restricted diffusion in the left frontal lobe (*A, arrow*) with associated enhancement seen on the coronal postcontrast image (*B, arrow*). Six months later there was improvement in the restricted diffusion (*C*) and contrast enhancement (*D*).

COMMENT

This case describes a clinical and imaging pattern indicative of SMART syndrome, a delayed complication from radiation therapy with spontaneous resolution with improved seizure control.

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CASE 8-3

A 60-year-old right-handed man with a history of coronary artery disease, hypertension, and hemorrhoids presented with several months of progressive proximal leg weakness. Imaging revealed an intradural intramedullary lesion at T11 and he underwent T10 to T12 laminectomy and subtotal resection of the lesion at T11 (FIGURE 8-3A and 8-3B) with pathology confirming a grade 2 ependymoma. He went on to receive fractionated radiation from T8 to L1 with a total of 5040 Gy in 28 fractions (FIGURE 8-3C and 8-3D).

Six months later, he developed worsening leg weakness and imaging revealed stable enhancement, but markedly increased cord T2 signal extending to C7 (FIGURE 8-3E and 8-3F). Given concern for radiation toxicity, he first received single doses of bevacizumab with significant improvement in symptoms and radiologic findings (FIGURE 8-3G and 8-3H).

COMMENT

This clinical and imaging pattern is an example of late radiation-induced myelopathy and radiation necrosis successfully treated with antiangiogenic therapy.

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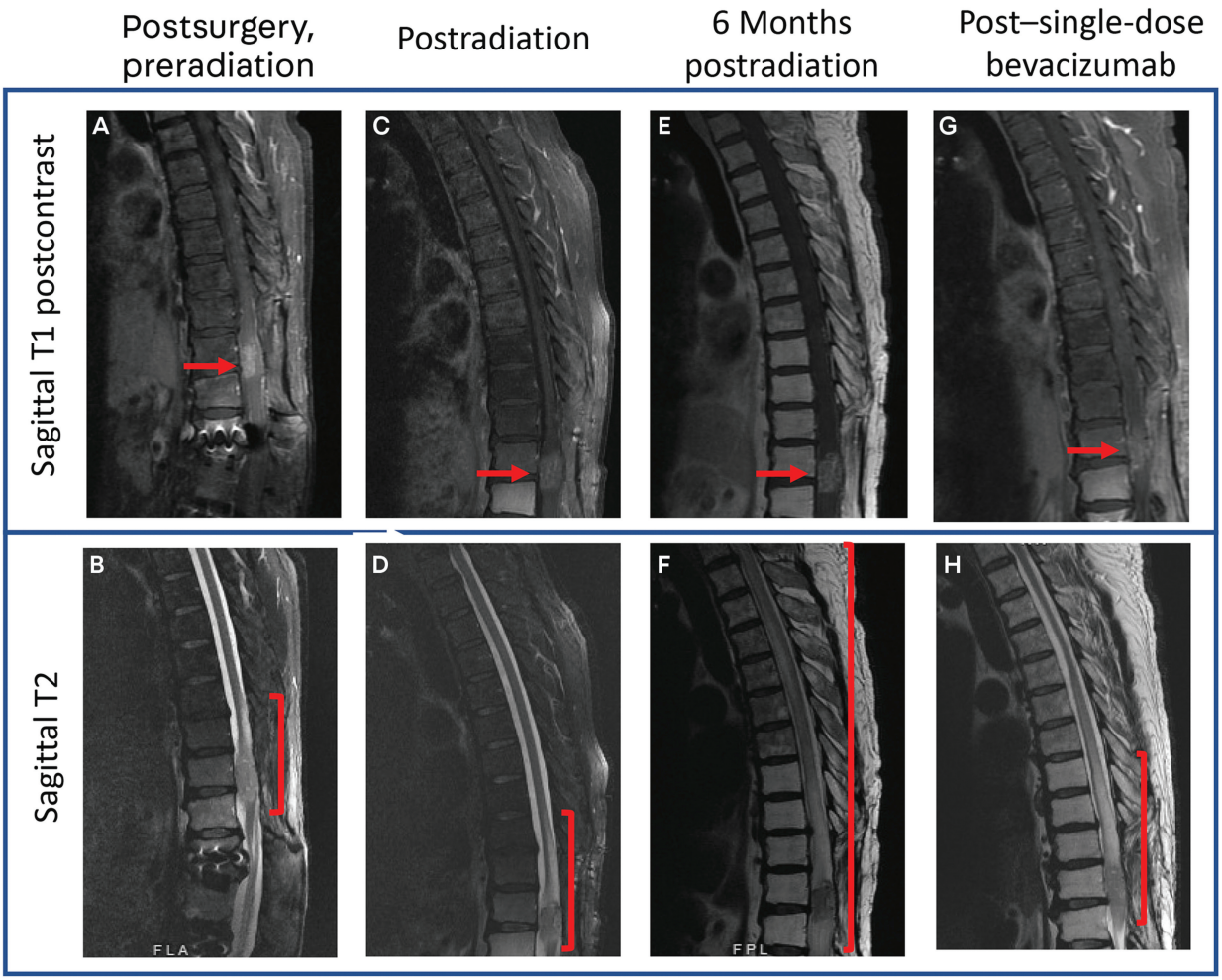

FIGURE 8-3

Imaging of the patient in CASE 8-3 shows sagittal spine MRI sequences suggestive of radiation necrosis following radiation therapy for spinal cord ependymoma. An intradural intramedullary enhancing mass is seen on postcontrast images (*A*) with surrounding edema (*B*). After radiation therapy, the enhancing lesion (*C*) and extent of edema (*D*) were stable; however, 6 months after radiation therapy there was stable enhancement (*E*) but increased edema (*F*) that improved after a single dose of bevacizumab (*G*, *H*). *Arrows* and *brackets* indicate the stable area of enhancement and the fluctuating extent of edema, respectively.

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The long-term cognitive effects of cranial irradiation, particularly whole-brain radiation therapy, are highly variable but can significantly impact survivorship. A better understanding of these deficits has led to efforts to minimize radiation exposure in pediatric patients, particularly children 5 years old and younger. Cognitive deficits in adult survivors of lung and other cancers have prompted the increasing use of stereotactic radiosurgery over whole-brain radiation therapy to treat brain metastases[39,40] and strategies for hippocampal sparing and concurrent use of memantine in patients for whom whole-brain radiation therapy is unavoidable.[41]

Given the impact of radiation on endothelial cells, cerebrovascular injury is a known long-term complication of radiation. Childhood radiation exposure can increase the risk of arteriopathy[42] and ischemic stroke[43] years to decades afterward and is particularly important to note when the radiation includes the circle of Willis or extracranial carotid arteries.

Strokelike Migraine Attacks After Radiation Therapy Syndrome

Another important long-term neurologic complication related to radiation is strokelike migraine attacks after radiation therapy (SMART) syndrome, a phenomenon that occurs years to decades after radiation exposure (CASE 8-2). Although its mechanism is poorly understood, both radiation-induced vascular alterations and neuronal hyperexcitability are involved.[44] Clinical symptoms include subacute onset of headaches, seizures, and focal neurologic symptoms.[45,46] Imaging confirms restricted diffusion, T1 postcontrast enhancement, and abnormal FLAIR signal. This constellation of clinical and radiologic findings can be difficult to distinguish from tumor recurrence and treatment is not standardized, although antiseizure medications are often indicated if seizures are confirmed. SMART syndrome can also recur.

Radiation-Induced Neuropathies, Plexopathies, and Myelopathy

The principles that apply to radiation-induced changes in the brain also apply to cranial and peripheral nerves and the spinal cord. Specific examples are discussed below.

OPTIC NEUROPATHY. Optic neuropathy is a potentially disabling complication of radiation therapy, manifesting as painless, progressive binocular or monocular visual loss. It often occurs 6 to 24 months after radiation therapy and, similar to other complications from radiation therapy, is impacted by higher fraction sizes.[47] Vision impairment rarely improves and there are no known effective treatments.

OTOTOXICITY. Ototoxic complications, including tinnitus and sensorineural hearing loss, are not uncommon in older patients and those for whom the auditory apparatus is within the high-dose treatment field. It occurs months to years after radiation therapy,[48] with the dose and concurrent chemotherapy increasing the risk. Tinnitus and high-frequency hearing loss can also occur acutely during treatment from radiation-induced otitis media but usually resolve.

Additional complications of cranial irradiation include cataracts and endocrine dysfunction, which can occur as early-delayed or long-term complications.

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PLEXOPATHIES. Brachial plexopathies are more common after radiation for lung or breast cancers but can be seen in any patient for whom the brachial plexus was included in the radiation field. Again, total dose, fraction size, and concurrent chemotherapy are all risk factors and symptom onset generally occurs around 1 year after radiation therapy.[49] Although frequently less painful than neoplastic plexopathy, the paresthesias and weakness can be severe. Fasciculation potentials and myokymic discharges seen on EMG favor a diagnosis of radiation-induced versus neoplastic plexopathy and treatment focuses on the management of neuropathic pain.[50]

Lumbosacral radiculoplexopathies are seen in patients who have received radiation to the pelvis. Similar to brachial plexopathies, symptoms include weakness and sensory loss and onset can occur months to years after treatment. Involvement is often bilateral, and the risk is higher with intracavitary and intraoperative versus external beam radiation therapy. In addition to myokymic discharges on EMG, which are suggestive of a radiation-associated mechanism versus neoplastic involvement, imaging can also be supportive with a lack of fludeoxyglucose uptake on PET.[51] Management is focused on neuropathic pain control, and physical therapists can help develop compensation strategies and recommend assistive devices.

MYELOPATHY. Myelopathy may be seen as a complication of radiation therapy involving the spinal cord. Early after radiation therapy, often within 6 months, patients may develop Lhermitte sign, and tumor progression, vitamin B_{12} deficiency, and other demyelinating diseases should be excluded.[52] Treatment is supportive and symptoms often resolve.

However, similar to other delayed complications from radiation, late radiation-induced myelopathy is a progressive myelopathy without proven treatments. Both wallerian degeneration from demyelination and vascular changes can lead to fibrinoid necrosis and hemorrhage.[53] The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) study, supported by the American Society for Radiation Oncology and the American Association of Physicists in Medicine, provided a thorough review of the risk of developing myelopathy based on total radiation dose, volume, and fraction,[54] and concurrent chemotherapy was also associated with increased risk. Symptom onset is insidious and occurs more than 6 months after treatment. Symptoms are often painless (versus spinal metastases) and may start with decreased sensation but can progress to a myelopathic pattern of weakness and bowel or bladder dysfunction, which rarely spontaneously resolve. Intramedullary hyperintensity on T2 with some focal enhancement is the most common MRI finding (CASE 8-3) and is usually correlated with the radiation treatment field, although over time distal atrophy develops and parallels the clinical myelopathic picture.[55] Treatment is similar to that for intracranial radiation necrosis, including glucocorticoids (with particular attention paid to the confounding risk of steroid myopathy) and bevacizumab.[36]

In addition to myelopathy, and similar to delayed complications from cranial irradiation, the development of vascular abnormalities such as telangiectasias and cavernous malformations can lead to hemorrhage and a sudden onset of worsening neurologic symptoms, which can be difficult to distinguish from tumor recurrence.[56]

KEY POINTS

- Strokelike migraine attacks after radiation therapy (SMART) syndrome is a delayed neurologic complication that often manifests as focal seizures and can be difficult to distinguish from tumor recurrence.
- Fasciculation potentials and myokymic discharges seen on EMG favor a diagnosis of radiation-induced versus neoplastic plexopathy.

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CONCLUSION

Neurologic complications are a common outcome of many cancer treatments. The CTCAE is an efficient grading system for the most common complications of systemic treatments and radiation therapy.[1] While some complications are acute, others are quite delayed and are increasingly important aspects of survivorship as patients with cancer live longer. Neurologists should be comfortable with recognizing and managing prevention strategies, early recognition, symptom management, and the impacts of cancer-directed therapies.

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Neurologic Complications of Cancer Immunotherapy

By Nancy Wang, MD, MPH

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **Immunotherapeutic approaches have revolutionized cancer treatment with immune checkpoint inhibitors and adoptive T-cell therapy now approved to treat a variety of solid and hematologic malignancies. This article summarizes the distinctive neurologic side effects of these therapies as well as their management.**

LATEST DEVELOPMENTS: **Neurologic immune-related adverse events are rare but potentially serious complications of immune checkpoint inhibitors. Both peripheral and central nervous system disorders have been described, often necessitating a pause or cessation of immunotherapy. Immune effector cell–associated neurotoxicity syndrome is a potentially serious complication of chimeric antigen receptor T-cell therapy. While symptoms may be mild and self-limited, delirium, encephalopathy, seizures, focal neurologic deficits, and fulminant cerebral edema can be seen. Close neurologic monitoring is imperative. The mainstay of treatment for neurologic complications includes high-dose corticosteroids, although other immunomodulatory strategies may be used in severe or refractory cases.**

ESSENTIAL POINTS: **The spectrum of neurologic complications of cancer immunotherapy is broad, encompassing both central and peripheral nervous system disorders, indolent as well as fulminant clinical presentations, and wide-ranging severity with variable response to treatment. Early identification and multidisciplinary management are crucial to balance neurologic recovery and antitumor control.**

INTRODUCTION

Immune-based approaches have dramatically altered the landscape of cancer treatment and raised unique neurologic considerations in their side-effect profile. Immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T-cell therapy are two forms of immunotherapy increasingly used to treat various malignancies. Their widespread clinical use underscores the importance of the recognition and management of common and sometimes fatal associated neurologic complications. The Common Terminology Criteria for Adverse Events (CTCAE) is a standardized grading system for adverse effects of cancer therapy, with grades 1 through 5 reflecting

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Dr Wang has received personal compensation in the range of $500 to $4999 for serving on a scientific advisory or data safety monitoring board for Seagen, Inc. The institution of Dr Wang has received research support from Merck & Co., Inc. Dr Wang has received royalties from a publication relating to health care.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Wang discusses the unlabeled/investigational use of anakinra, antithymocyte globulin, and siltuximab for the treatment of immune effector cell–associated neurotoxicity syndrome.

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increasing severity that ranges from mild or asymptomatic to death related to the adverse effect. Immunotherapeutic strategies such as oncolytic viruses, vaccines against tumor-associated antigens, and other immunomodulators are also under active investigation.[1-3] However, given the relative paucity of data regarding neurologic complications of these agents, this review focuses on ICIs and adoptive T-cell therapy.

IMMUNE CHECKPOINT INHIBITORS

ICIs are now widely used to treat many types of cancer and can cause distinctive and potentially devastating neurologic side effects. This section covers the evaluation and management of immune-related neurologic adverse effects of ICIs, both peripheral and central.

Background

ICIs are monoclonal antibodies that regulate the activation of the innate and adaptive immune systems by modulating the activation of naive T-cells. By interfering with inhibitory signals, ICIs can restore and boost cytotoxic T-cell activity, leading to therapeutic efficacy across many types of cancer, including melanoma, lung, breast, colorectal, renal, bladder, and head and neck cancer, and any solid tumor with mismatch repair deficiency or high tumor mutational burden. Since the authorization of the first ICI in 2011, ipilimumab, which binds to cytotoxic T-lymphocyte antigen 4 (CTLA-4), there are now approved agents targeting programmed cell death 1 (PD-1), programmed death-ligand 1 (PD-L1), and lymphocyte-activation gene 3, with drugs against other targets, such as TIGIT and GITR, in clinical trials.[4]

Despite the broad use of ICIs, the distinct side-effect profile remains a clinical challenge. Side effects to checkpoint inhibitors, also known as immune-related adverse events, occur as a result of T-cell activation leading to an inflammatory reaction. While the exact mechanisms are not fully understood, immune-related adverse events are thought to be mediated by T-cell activity against antigens expressed in normal tissue, increased titers of preexisting autoimmune

TABLE 9-1 **Type and Frequency of Immune-related Neurologic Adverse Events[a]**

- **Central nervous system (CNS) demyelinating diseases: 8/428 (2%)**
- **Cranial neuropathies: 31/428 (7%)**
- **Encephalitis: 56/428 (13%)**
- **Meningitis: 13/428 (3%)**
- **Myasthenic syndromes: 58/428 (14%)**
- **Myelitis: 7/428 (2%)**
- **Myositis: 136/428 (32%)**
- **Neuropathies: 94/428 (22%)**
- **Other CNS syndromes: 25/428 (6%)**

[a] Data from Marini et al, Neurology.[6]

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antibodies, increased levels of proinflammatory cytokines, or activation of the complement system.[5]

Neurologic immune-related adverse events are well described and may affect both the central and peripheral nervous systems (TABLE 9-1[6]). The incidence of neurologic immune-related adverse events is estimated at 1% to 5% for monotherapy against CTLA-4 and PD1 or PD-L1 and approximately 12% for combination therapy.[5,7] While neurologic immune-related adverse events are relatively rare compared to other immune-related adverse events, they account for up to 15% of all ICI-related fatalities. Neurologic complications are more commonly reported in the setting of melanoma, non–small cell lung cancer, combination anti-PD1 or PD-L1 and anti-CTLA-4 therapy, and in older individuals.[5,8,9] There is also an association between female sex and meningitis, encephalitis, myelitis, and demyelinating disorders among patients on these agents.[9] Neurologic complications tend to arise within the first 6 months of treatment, and symptom onset over 12 months from the last ICI infusion should prompt workup for alternate etiologies.[10,11] The peripheral nervous system is affected more frequently than the central nervous system, with neuromuscular disorders accounting for over 50% of neurologic immune-related adverse events in some cohorts.[12] TABLE 9-2 summarizes the peripheral and central nervous system neurologic syndromes associated with ICI use. Accurate and rapid diagnosis of the clinical syndrome and initiation of anti-inflammatory, immunosuppressive treatment is crucial to neurologic recovery.

Clinical Evaluation

There are multiple published guidelines regarding the definitions, diagnosis, severity grading, and management of neurologic immune-related adverse events, although data from prospective trials are lacking.[11,13,14] Patients on ICIs presenting with neurologic symptoms should undergo a thorough workup, including careful assessment for possible preexisting neurologic disorders. Other

Neurologic Syndromes Associated with Immune Checkpoint Inhibitors TABLE 9-2

Central nervous system

- Encephalitis
- Meningitis
- Central nervous system demyelinating disease
- Myelitis
- Vasculitis

Peripheral nervous system

- Myositis
- Myasthenia gravis
- Demyelinating polyradiculoneuropathy
- Cranial neuropathies
- Other peripheral neuropathies (eg, demyelinating polyneuropathy, mononeuritis multiplex, small fiber neuropathy, sensory neuronopathy)

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broad considerations include tumor progression, vascular complications (eg, ischemia, hemorrhage), infection, toxic or metabolic disorders, or side effects from other systemic therapies. Immune-related adverse events often involve multiple organ systems, and the presence of one immune-related adverse event or neurologic immune-related adverse event warrants consideration of overlapping disease patterns, such as myositis and myocarditis.

Diagnostic studies can include laboratory studies to evaluate for toxic or metabolic abnormalities, including pituitary and endocrinologic dysfunction, infectious studies, imaging, CSF analysis, EEG, and EMG. Serology and CSF testing for autoimmune antibodies can be helpful as well. Some neurologic immune-related adverse events are associated with known autoimmune antibodies, such as antiacetylcholine receptor antibodies in myasthenic syndromes. However, it can be difficult to distinguish symptoms from an ICI-driven antibody-mediated process versus a paraneoplastic syndrome. While the workup and management often overlap, there may be significant treatment implications and multidisciplinary discussion is imperative in weighing the risks and benefits of therapy.

Peripheral Nervous System Effects

ICI-related neuromuscular syndromes overlap significantly with non–ICI-related disorders affecting the peripheral nervous system. However, management and response to treatment may differ.

MYOPATHY. Myopathies are the most common neuromuscular adverse event associated with ICIs and include necrotizing myositis, dermatomyositis, and polymyositis. Typically occurring within the first 3 months of therapy, presenting symptoms include muscle pain and progressive weakness, often proximal in distribution. Oculobulbar weakness is a common feature and may be the predominant or sole presentation in nearly one-half of patients with ICI-induced myopathy, mimicking myasthenia gravis.[12] Workup often reveals elevated blood creatinine kinase levels (although they may be normal or mildly elevated) and striational antibodies may be present. Electrodiagnostic testing is diagnostically helpful and may reveal myopathic changes with fibrillation potentials on needle EMG. Muscle MRI and positron emission tomography (PET) scans are abnormal with evidence of fasciitis, muscle T2 hyperintensity, muscle enlargement, or fludeoxyglucose uptake in approximately one-half of patients.[12] Paraspinal and masticatory muscles are most commonly affected, even in patients without reported neck extensor weakness. Thus, imaging may be helpful in situations where the muscles are not accessible or needle EMG is not routinely performed. Muscle biopsy typically demonstrates infiltration with lymphocytes, necrotic fibers, or both in a multifocal cluster.[12,15] As many as 30% of patients with ICI-induced myositis may also have myocarditis, and thus the presence of one should prompt workup for the other with detailed clinical history, evaluation of cardiac troponins, ECG, and possibly cardiac imaging.[13,16] ICI-induced rheumatologic disorders such as polymyalgia rheumatica and inflammatory arthritis should also be considered. Nonspecific fatigue, headache, or vision changes should also prompt evaluation for hypophysitis with pituitary axis assessment and pituitary protocol MRI.

Treatment typically consists of steroids along with cessation of the ICI. Response is usually favorable, although limited data exist on the safety of ICI

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rechallenge and ICI therapy should be discontinued for CTCAE grade 2 or higher toxicity. Intubation and concurrent myocarditis have been reported as poor prognostic factors and myopathy-associated mortality is estimated at around 20%.[12,17]

MYASTHENIA GRAVIS. While one case of Lambert-Eaton myasthenic syndrome has been reported, myasthenia gravis constitutes the vast majority of neuromuscular junction disorders associated with ICI use.[18] Presenting symptoms include exercise-dependent fluctuating weakness involving the proximal extremities, bulbar dysfunction, or ocular symptoms. Approximately one-half to two-thirds of patients are positive for antiacetylcholine receptor antibodies.[13,15] Negative antiacetylcholine receptor antibodies should prompt evaluation for antibodies against muscle-specific kinase (MuSK) and lipoprotein receptor–related protein 4. Given the potential for clinical overlap, evaluation for myositis, thyroid dysfunction, and myocarditis should also be conducted. Myasthenic symptoms are more commonly associated with PD-1 blockade than anti-CTLA-4 therapy and most often emerge within the first few months of therapy.[19] Treatment involves high-dose steroids (eg, methylprednisolone), pyridostigmine, and, in severe cases, intravenous immunoglobulin (IVIg), plasma exchange, or both.

While symptoms typically respond to steroids and other therapies with complete resolution in up to 50% of patients, cessation of ICIs is often warranted as ICI-associated myasthenia gravis has been associated with a mortality rate as high as 30%, typically from respiratory failure.[6,15,16,19] The clinical course may also be more fulminant than non-ICI-related myasthenia gravis, with a reported time from first myasthenic symptom to respiratory failure as low as 7 days.[20,21] Additional data are needed to assess the safety of ICIs in patients with preexisting myasthenia gravis, the treatment of cases refractory to IVIg and plasma exchange, and if or when these patients may be rechallenged with ICIs.

PERIPHERAL NEUROPATHY AND POLYRADICULONEUROPATHY. The incidence of immune-mediated neuropathies is generally estimated at less than 1% of patients on ICI therapy with a wide range of phenotypes reported, including demyelinating, immune-mediated neuropathy, small fiber neuropathy, mononeuritis multiplex, neuralgic amyotrophy, sensory neuronopathy, length-dependent sensorimotor axonal polyneuropathy, isolated cranial neuropathy (most commonly facial or optic nerves), enteric neuropathy, and autonomic ganglionopathy.[22,23] In comparison to chemotherapy-induced peripheral neuropathy, immune-related neuropathies are more likely to be acute or subacute in onset and non–length dependent in anatomic distribution.[6] Both acute inflammatory polyradiculoneuropathy (AIDP) and chronic inflammatory demyelinating polyneuropathy (CIDP) have been reported. Clinical symptoms may include bilateral proximal weakness, ataxia, areflexia, sensory and autonomic disturbances, and cranial nerve palsies.[24] CSF analysis often reveals cytoalbuminologic dissociation and antiganglioside antibodies are often negative.[13] Imaging may reveal nerve root or peripheral nerve enhancement. CSF examination and brain MRI are abnormal in approximately 60% to 70% of patients with cranial neuropathies.[6]

In contrast to classic AIDP, ICI-related AIDP often responds favorably to corticosteroids, which are considered first-line treatment. IVIg may be

KEY POINTS

- Neurologic immune-related adverse effects can affect both the central and peripheral nervous systems, although peripheral complications are more common.
- The incidence of neurologic immune-related adverse effects is higher for combined anti–cytotoxic T-lymphocyte antigen 4 and anti–programmed cell death 1 or programmed death-ligand 1 therapy than monotherapy.
- Neurologic complications of immune checkpoint inhibitors tend to arise within the first 6 months of treatment.
- The presence of one immune-related adverse event or neurologic immune-related adverse effect should prompt evaluation for overlapping syndromes, such as myositis and myocarditis.
- Myopathy and myasthenia gravis are two common peripheral nervous system complications of immune checkpoint inhibitors. While response to steroids and other therapies is typically favorable, associated mortality rates are as high as 20% to 30%.
- In contrast to chemotherapy-induced neuropathy, immune checkpoint inhibitor-related neuropathies are more often acute or subacute in onset and non–length dependent in distribution.

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considered in some cases. Interruption of ICI therapy is indicated for CTCAE grade 2 or higher symptoms, with consideration of permanent discontinuation for higher-grade symptoms or if symptoms do not improve with drug hold. Approximately 70% to 90% of patients achieve partial or complete recovery.[6] CASE 9-1 demonstrates the importance of early recognition, workup, and treatment to facilitate recovery.

Central Nervous System Effects

ICI-related central nervous system adverse effects are less common and response to treatment is generally favorable. Infectious and other immune-related disorders such as paraneoplastic syndromes should be considered in the differential.

ENCEPHALITIS. Presenting symptoms of encephalitis commonly include altered mental status, cognitive impairment, seizures, psychiatric disturbances, and movement disorders. While fluid-attenuated inversion recovery (FLAIR) hyperintensity of the mesial temporal lobes on MRI is the most commonly

CASE 9-1

A 73-year-old woman with a history of small cell lung cancer presented with several months of progressive numbness, pain, and weakness. Her symptoms started several weeks after initiation of atezolizumab (a humanized monoclonal antibody against programmed death-ligand 1) for her lung cancer, initially described as numbness and tingling in the fingers and feet, and subsequently progressing to shooting pain in the extremities and bilateral lower limb weakness. Examination revealed bilateral proximal lower limb weakness, 2/5 in hip flexion, as well as more generalized 4/5 weakness. There was decreased sensation to light touch and temperature in a length-dependent distribution as well as marked allodynia to vibration testing. Reflexes were absent throughout.

Nerve conduction studies and EMG demonstrated a myopathy as well as a length-dependent axonal sensorimotor polyneuropathy, felt to be immune-related due to the temporal association with immune checkpoint inhibitor (ICI) therapy. She was treated with 3 days of IV methylprednisolone while an inpatient, followed by a prednisone taper over 8 weeks to minimize steroid-induced hyperglycemia and maximize outpatient recovery. While steroids led to the resolution of her neuropathic pain, improvement plateaued and she continued to have significant weakness that impaired her mobility. She was started on intravenous immunoglobulin (IVIg) which resulted in the return of sensation in her feet and improved strength. Atezolizumab was permanently discontinued.

COMMENT

This case demonstrates the potential for more than one neurologic adverse effect in patients on ICI therapy, in this case a combined length-dependent peripheral neuropathy and myopathy, and the importance of early recognition for treatment and neurologic recovery.

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reported imaging abnormality, similar to idiopathic or infectious limbic encephalitis, imaging may also be normal. Other reported imaging abnormalities include basal ganglia and cortico-subcortical hyperintensities.[6] CSF examination is abnormal in over 90% of patients, with characteristic findings including pleocytosis and elevated protein. Importantly, causes of infectious encephalitis such as herpes simplex virus and varicella-zoster virus should be excluded. Serologic evaluation is notable for elevated autoimmune antibodies in up to one-half of patients, with reported antibodies including anti-Ma2, antineuronal nuclear antibody type 1 (Hu), anti–glutamic acid decarboxylase 65 (GAD65), and anti–*N*-methyl-D-aspartate (NMDA).[6,25,26] Due to the potential presence of nonpathogenic autoimmune antibodies secondary to ICI use and overlap with paraneoplastic syndromes, the interpretation of antibodies must be done in a clinical context. Other diagnostic considerations include brain metastases, hypophysitis, toxic metabolic encephalopathy, stroke, and vasculitis. EEG monitoring may be helpful to rule out subclinical seizures.

Treatment consists of discontinuation of ICIs, high-dose IV methylprednisolone (typically for 5 days), and IVIg or plasmapheresis in severe cases. The use of rituximab and natalizumab has also been reported, although due to the small number of cases the efficacy remains unclear.[26,27] While the majority of patients have partial or complete response, the mortality rate is approximately 20%.[6] Early recognition and treatment with high-dose steroids likely result in more favorable outcomes.

MENINGITIS. Meningitis is the second most common central neurologic immune-related adverse event and is more commonly associated with anti-CTLA-4 agents. Female sex and younger age have been identified as risk factors.[9] Time to onset is typically shorter than for other neurologic immune-related adverse events, with median onset after two cycles and a delay of 9 days from the last infusion.[28,29] Symptoms of ICI-related aseptic meningitis include altered mental status, headache, photophobia, nausea, and vomiting. Motor or sensory symptoms such as myoclonus, ataxia, or paresthesias are less commonly reported. Autoimmune antibodies are typically not detected, and CSF analysis generally shows significant lymphocytic pleocytosis, elevated protein, and normal glucose. Opening pressure may also be elevated. Imaging features include sulcal FLAIR hyperintensity or enhancement and nerve root enhancement. Similar to encephalitis, the exclusion of infectious causes is essential, particularly for common pathogens such as herpes simplex virus and cryptococcus. Evaluation for leptomeningeal metastasis should also be considered with CSF testing for cytology, flow cytometry, or tumor markers.

The initiation of steroids typically leads to a response within days; however, the use of IVIg and infliximab has also been described in more refractory cases.[29] Prognosis is excellent with complete recovery in the vast majority of patients. The reintroduction of ICIs may be possible in patients with immune-related meningitis; however, rechallenge with anti-CTLA-4 therapy is more controversial due to the increased association with meningitis. CASE 9-2 illustrates a patient with aseptic meningitis secondary to combined anti-PD-1 and anti-CTLA-4 therapy who was subsequently successfully treated with anti-PD-1 therapy alone.

CENTRAL NERVOUS SYSTEM DEMYELINATING DISEASE. ICIs have been reported to cause both exacerbation of preexisting multiple sclerosis and de novo central

KEY POINTS

- Encephalitis and meningitis are the two most common central nervous system complications of immune checkpoint inhibitors, which should be distinguished from infectious causes.
- Autoimmune antibodies are elevated in up to one-half of patients with immune checkpoint inhibitor–related encephalitis. However, interpretation should be made in the appropriate clinical context given the possibility of nonpathogenic antibodies and paraneoplastic disorders.

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nervous system demyelination. The course of new-onset cases is typically monophasic without relapses after ICI discontinuation, and response is favorable to steroids alone or in combination with other therapies.[6] Asymptomatic lesions with spontaneous regression after cessation of checkpoint inhibitors have also been reported.[30] Additionally, cases of longitudinally extensive transverse myelitis with positive anti–aquaporin-4 (AQP4) antibodies have been described, and serologic testing for anti-AQP4 and anti-myelin oligodendrocyte glycoprotein antibodies should be performed in suspected cases of demyelinating disease. Brain and spine imaging shows characteristic demyelinating lesions, and CSF typically shows modestly elevated cell count and elevated protein. The presence of oligoclonal bands and an elevated IgG index are also supportive of

CASE 9-2

A 46-year-old man with metastatic melanoma who had recently started taking ipilimumab and nivolumab presented for the evaluation of headaches. One week after his first infusion he developed inflammatory arthritis. Ten days later he developed severe bitemporal headache and a fever of 39.3°C (102.7°F). His mental status was normal and there were no other associated neurologic symptoms. His neurologic examination was normal. A brain MRI was unrevealing, and a lumbar puncture showed an elevated opening pressure of 26 cm H_2O, elevated total protein of 75 mg/dL, and 92 nucleated cells with lymphocytic predominance and abundant monocytes. Infectious workup was negative. Given the bitemporal quality of his headache and elevated serum inflammatory markers, he underwent a temporal artery biopsy to evaluate for giant cell arteritis, which was unremarkable. His fever resolved with acetaminophen and his headaches resolved in 3 days with conservative management. Corticosteroids were not initiated.

After his second cycle of ipilimumab and nivolumab, he developed headaches the day following the infusion, although overall they were less severe than after the first cycle. He was treated conservatively with IV hydration and oral analgesics with good response and his headaches improved within 5 days without steroids. Additional ipilimumab and nivolumab were ultimately withheld due to biopsy-proven autoimmune hepatitis which required a prolonged steroid taper. The patient subsequently started maintenance nivolumab monotherapy and tolerated the treatment well without recurrent headaches.

COMMENT

While steroids and immunosuppression remain the mainstay of treatment for neurologic immune-related adverse effects, conservative management with supportive care without steroids and with a pause in therapy can also be considered in the appropriate setting. A workup should include consideration of other potential causes, such as infection or other immune-related adverse effects such as vasculitis or hypophysitis. This case illustrates the potential for successful rechallenge in immune checkpoint inhibitor–induced meningitis, particularly with anti–programmed cell death 1–directed therapy.

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the diagnosis. An ophthalmic examination to assess for optic neuritis may be considered.

MYELITIS. Patients with ICI-associated myelitis present with typical features of paraparesis, sphincter dysfunction, sensory disturbances, and proprioceptive ataxia. Imaging typically reveals T2 hyperintense lesions in the spinal cord with associated patchy enhancement. Concurrent abnormalities involving brain parenchyma, meninges, caudal nerve roots, or peripheral nerves are common.[31] While anti-AQP4 and anti–myelin oligodendrocyte glycoprotein antibodies should be checked, only positive anti-AQP4 antibodies have been reported in patients with longitudinally extensive transverse myelitis. Response to high-dose corticosteroids and other immunomodulatory agents is generally favorable, although relapses have been reported, and in one case series only 43% of patients regained ambulatory status.[31] Thus, patients with longitudinally extensive myelitis may benefit from more aggressive upfront immunomodulatory therapy. While there are little data to guide management, reported second-line treatments include plasmapheresis, IVIg, cyclophosphamide, infliximab, rituximab, natalizumab, and tocilizumab.[31]

VASCULITIS. ICI-associated vasculitis involving cervical and cranial vessels may lead to strokes or other parenchymal findings on imaging. Cerebral vasculitis mimicking a brain metastasis after PD-1 inhibitor treatment has also been reported.[32] A systematic review of ICI-associated vasculitis found that large vessel vasculitis (eg, giant cell arteritis) and vasculitis of the central and peripheral nervous systems were the most common, with all cases resolving with cessation of ICIs or use of corticosteroids.[33] Vascular imaging with MR angiography (MRA) or CT angiography and the inclusion of postcontrast vessel wall studies when available should be performed and may show concentric vessel wall enhancement, narrowing, or beaded vessels. Other causes of vasculitis such as varicella-zoster virus should be considered, and a stroke workup should be performed if ischemic injury is present. Serologic testing for c-reactive protein, erythrocyte sedimentation rate, antineutrophil cytoplasmic antibody, and antinuclear antibody may further support the diagnosis. Rheumatologic or dermatologic evaluation may be considered to evaluate for systemic vasculitis. In the setting of neurologic symptoms, imaging abnormalities, and concern for CNS vasculitis, CSF evaluation should be pursued.

ADOPTIVE T-CELL THERAPY

CAR T-cell therapies are now commonly used in hematologic malignancies, although complications such as cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome (ICANS) are common. This section discusses the diagnosis and management of CAR T-cell–related neurotoxicity.

Background

CAR T-cell therapy employs a patient's own T-cells, which are harvested and genetically engineered to express CARs that allow the T-cells to activate upon recognizing specific antigens on tumor cells. Approved CAR T-cell therapies target CD19 (ie, tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, and lisocabtagene maraleucel) and B-cell maturation antigen (ie, idecabtagene vicleucel and ciltacabtagene autoleucel) on neoplastic B cells.

KEY POINTS

- Immune effector cell–associated neurotoxicity syndrome (ICANS), previously known as *cytokine release encephalopathy syndrome*, can occur in up to 50% of patients treated with chimeric antigen receptor (CAR) T-cell therapy.
- Immune effector cell–associated neurotoxicity syndrome (ICANS) is associated with earlier onset and higher severity of cytokine release syndrome. The presentation is biphasic with the first peak within 5 days of chimeric antigen receptor (CAR) T-cell administration, often occurring with cytokine release syndrome, and a second delayed peak occurring 3 to 4 weeks later.
- The immune effector cell–associated neurotoxicity syndrome (ICANS) grade is used to assess the severity of neurologic symptoms. Neuroimaging should be performed in patients with grade 2 or higher ICANS.
- Long-term neurologic effects after chimeric antigen receptor (CAR) T-cell therapy are now being described and include cerebrovascular complications, neuropsychiatric disturbances, and movement disorders.

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Genetically engineered T-cells have demonstrated remarkable success in treating hematologic malignancies with ongoing studies in solid tumors as well. However, they can trigger a systemic inflammatory state termed cytokine release syndrome as well as potentially severe ICANS, previously known as cytokine release encephalopathy syndrome.[34,35] While ICANS is seen in as many as 50% of patients receiving CAR T-cell therapy, the possibility of severe neurologic consequences such as fatal cerebral edema warrants close neurologic monitoring.

Cytokine Release Syndrome

A well-described phenomenon associated with CAR T-cell therapy is cytokine release syndrome, which is associated with the secretion of inflammatory cytokines such as interleukin-6 (IL-6), interleukin-2, interferon gamma, and granulocyte-macrophage colony-stimulating factor. The clinical manifestations consist of fever, hypotension, and hypoxia, potentially progressing to multiorgan failure. Severity is graded 1 through 4 according to the American Society for Transplantation and Cellular Therapy cytokine release syndrome grading system.[34] Treatment of cytokine release syndrome, which typically occurs within the first week of CAR T-cell administration, consists of the IL-6 and IL-6 receptor antagonists siltuximab and tocilizumab, respectively, as well as corticosteroids.[36]

Immune Effector Cell–Associated Neurotoxicity Syndrome

ICANS is a distinct entity that is correlated with earlier onset and higher severity of cytokine release syndrome.[37] The clinical presentation tends to be biphasic with the first peak within 5 days of CAR T-cell administration, often occurring with cytokine release syndrome, and a second delayed peak occurring 3 to 4 weeks later. The first phase is typically less severe, lasts 2 to 4 days, and tends to be more responsive to anti-IL-6 therapy as opposed to the more protracted second phase for which steroids are the preferred management.[36] The underlying pathophysiology remains unclear; however, ICANS is thought to be mediated by cytokines and levels of CAR T cells entering the central nervous system with resulting endothelial activation and cortical dysfunction.[37,38] Patients with ICANS tend to have increased levels of CAR T cells, inflammatory cytokines, protein, and excitatory agonists in the CSF, suggesting disruption of the blood-brain barrier.[37,39]

TABLE 9-3 **Immune Effector Cell–Associated Encephalopathy Score**

Question type	Question examples	Points[a]
Orientation	Year, month, city, hospital	4
Naming	Three objects	1 point each
Commands	Ability to follow a simple command	1
Writing	Write a sentence	1
Attention	Count backward from 100 by 10	1

[a] Points are awarded for normal function, and thus a higher score is better.

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Factors influencing the risk and presentation of ICANS include the CAR T-cell target antigen, costimulatory domains, CAR T-cell dose, conditioning chemotherapy regimen, prior therapies, preexisting neurologic morbidity, older patient age, and timing and severity of cytokine release syndrome.[37-39] There is increased severity associated with leukemia and more aggressive types of lymphoma, as well as a high disease burden. One study showed that early, aggressive treatment with tocilizumab, which does not cross the blood-brain barrier, for cytokine release syndrome is associated with increased risk and severity of neurotoxicity, possibly by antagonizing peripheral activation of IL-6 receptors and thereby potentiating the central effects of IL-6.[40]

Clinical Evaluation

Close neurologic monitoring is required in patients receiving CAR T-cell therapy so that early signs of neurologic dysfunction can be promptly identified and

American Society for Transplantation and Cellular Therapy ICANS Consensus Grading for Adults[a,b] TABLE 9-4

Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[c]	7-9	3-6	0-2	0
Level of consciousness[d]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Stupor or coma: unarousable or requires vigorous or repetitive tactile stimuli to arouse
Seizure	N/A	N/A	Clinical seizure (focal or generalized) that resolves rapidly *OR* nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 minutes) *OR* repetitive clinical or electrographic seizures without return to baseline in between
Motor findings[e]	N/A	N/A	N/A	Focal motor weakness such as hemiparesis or paraparesis
Elevated ICP or cerebral edema	N/A	N/A	Focal edema on neuroimaging[f]	Diffuse cerebral edema on imaging *OR* decerebrate or decorticate posturing *OR* cranial nerve VI palsy *OR* papilledema *OR* Cushing triad (bradycardia, irregular respiratory pattern, and widened pulse pressure)

EEG = electroencephalogram; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; ICP = intracranial pressure.

[a] Modified from Lee DW, et al, Biol Blood Marrow Transplant.[34] © 2018 American Society for Blood and Marrow Transplantation.

[b] ICANS grade is determined by the most severe domain not attributable to another cause. Grade 5 ICANS is defined as death due to ICANS.

[c] A patient with an ICE score of 0 due to global aphasia can be classified as grade 3 ICANS, whereas a patient who is unarousable with an ICE score of 0 should be classified as grade 4 ICANS.

[d] Depressed level of consciousness should not be attributable to other causes (eg, sedating medication).

[e] Tremors or myoclonus are not included in ICANS grading and may be graded according to Common Terminology Criteria for Adverse Events v5.0.

[f] Intracranial hemorrhage is not included in ICANS grading and may be graded according to Common Terminology Criteria for Adverse Events v5.0.

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CASE 9-3

A 42-year-old woman with relapsed refractory high-grade B-cell lymphoma was admitted for chimeric antigen receptor (CAR) T-cell therapy with axicabtagene ciloleucel. She developed grade 1 cytokine release syndrome on postinfusion day 8. On day 9, she became encephalopathic with limited verbal output and her Immune Effector Cell–Associated Encephalopathy score was 1 for the ability to follow basic commands. Her neurologic examination was otherwise unrevealing. Head CT was normal, and she was started on dexamethasone 10 mg every 6 hours. However, her mental status continued to decline, and on day 10 she became somnolent, prompting transfer to the neurologic intensive care unit and initiation of levetiracetam. Repeat head CT and brain MRI were unremarkable, and she was empirically treated with multiple antimicrobial agents for possible infection. On day 13, she developed right facial twitching, although EEG did not reveal any epileptiform discharges or seizures; her levetiracetam dose was empirically increased. Repeat head CT on day 14 showed new sulcal and ventricular effacement as well as bilateral thalamic hypoattenuation (FIGURE 9-1A and 9-1B). The patient was started on hypertonic saline and mannitol, IV methylprednisolone 1000 mg daily for 3 days, siltuximab, and cyclophosphamide. Repeat head CT demonstrated new subarachnoid hemorrhage in the setting of thrombocytopenia. Repeat brain MRI on day 21 demonstrated diffuse cerebral edema, leptomeningeal enhancement, and cortical restricted diffusion (FIGURE 9-1C through 9-1F). Her examination continued to deteriorate with loss of brainstem reflexes and development of Cushing response. After goals of care discussions with her family, the patient was transitioned to comfort measures.

COMMENT

This case illustrates the potentially fulminant and fatal effects of immune effector cell-associated neurotoxicity syndrome. While presenting symptoms are often mild and nonspecific, close neurologic monitoring is imperative and aggressive supportive measures should be taken in the setting of neurologic decline. This case also illustrates the challenges of empiric treatment in patients who are medically ill as well as the often conflicting considerations of managing side effects and not abrogating the effectiveness of CAR-T cell therapy. While the patient was started on high-dose dexamethasone right away, broad-spectrum antimicrobial agents were added for possible infection in an immunocompromised state when there was no clinical improvement to initial corticosteroids. More aggressive immune-directed therapy was not pursued until repeat imaging for clinical progression showed diffuse cerebral edema. Dexamethasone should be initiated for grade 2 or higher immune effector cell-associated neurotoxicity syndrome (ICANS) and high-dose methylprednisolone for grade 4 or higher ICANS, and cerebral edema should be managed according to standard clinical practice. The use of other immunomodulatory strategies remains off label, investigational, and institution dependent.

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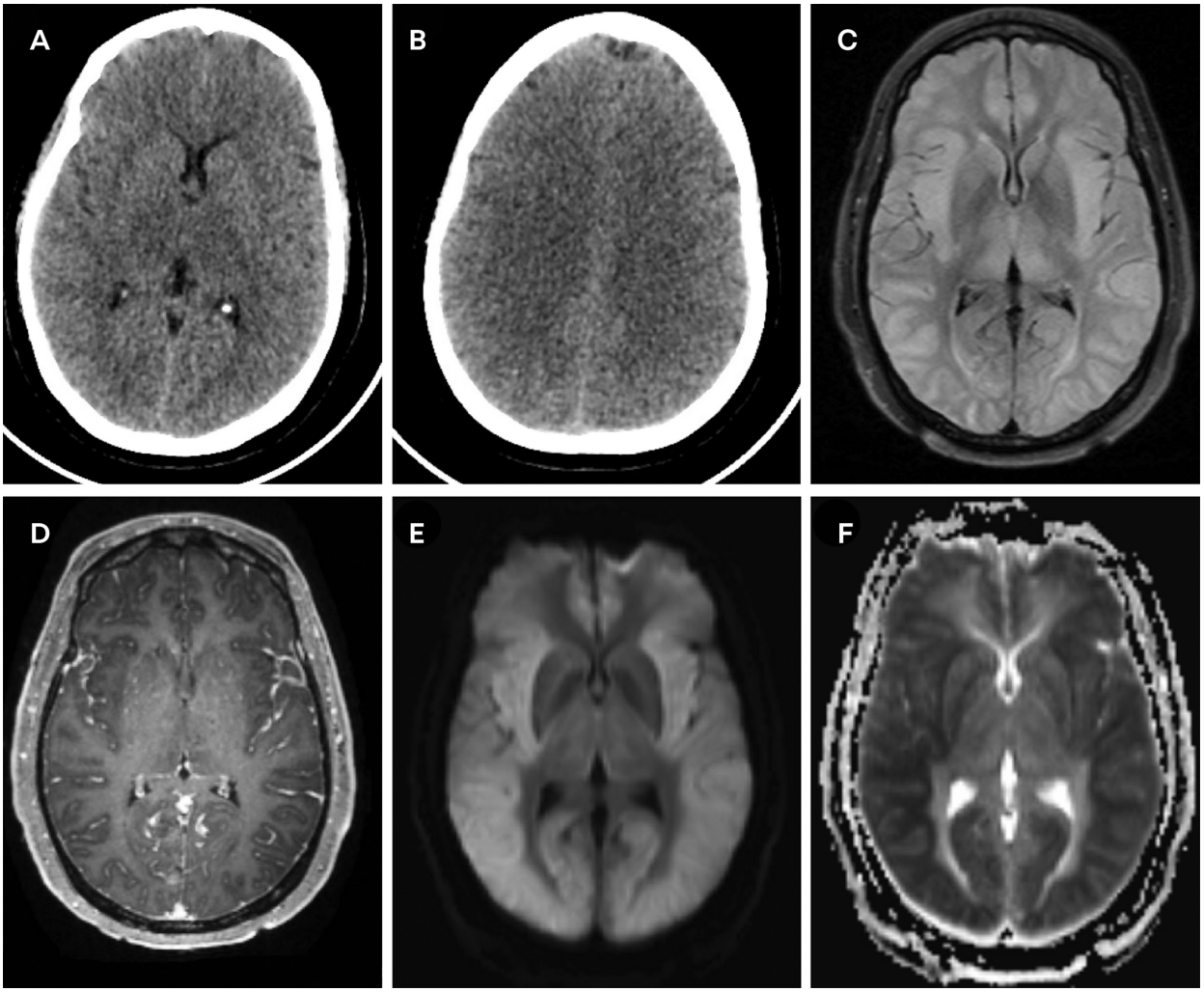

FIGURE 9-1

Imaging of the patient in CASE 9-3. *Panels A* and *B* were taken on day 14 post–chimeric antigen receptor T-cell infusion, and *panels C* through *F* correspond to brain MRI performed on postinfusion day 21. *A*, Axial noncontrast head CT demonstrating bilateral thalamic hypoattenuation. *B*, Axial noncontrast head CT showing diffuse sulcal effacement. *C*, Axial fluid-attenuated inversion recovery (FLAIR) image showing diffuse cerebral edema involving the cerebral cortex as well as white matter and thalami. *D*, Postcontrast T1-weighted image demonstrating diffuse leptomeningeal enhancement. *E*, Diffusion-weighted imaging MRI sequence demonstrating cortical restricted diffusion. *F*, Apparent diffusion coefficient MRI sequences demonstrating cortical restricted diffusion.

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managed. Early symptoms may include confusion, disorientation, agitation, aphasia, and tremor, which can progress to seizures, motor weakness, and obtundation.[36] Severity is graded using the CTCAE score, which is based on symptoms such as level of consciousness, orientation, headache, speech, tremors, and seizures, with a focus on the impact on activities of daily living.[41] A CAR T-cell–specific grading scheme was recently developed based on the Immune Effector Cell–Associated Encephalopathy (ICE) score (TABLE 9-3), which is adapted from the CAR T-Cell Therapy–Associated Toxicity (CARTOX-10) test. The ICANS grade is determined by the ICE score, level of arousal, seizure severity, motor deficits, and evidence of elevated intracranial pressure (TABLE 9-4).[34]

Diagnostic workup for these disorders includes evaluation for other causes of toxic or metabolic encephalopathy, such as infection or electrolyte abnormalities. Serum biomarkers such as c-reactive protein, ferritin, procalcitonin, fibrinogen, and IL-6 may have prognostic value in determining the clinical trajectory.[40] A lumbar puncture may be considered to assess for infection and elevated intracranial pressure; however, the risk of such a procedure needs to be carefully weighed. EEG may detect epileptiform discharges or nonconvulsive electrographic seizures, although generalized slowing is most commonly noted.[37,42] Patients with grade 2 or higher ICANS should undergo neuroimaging to assess for structural pathology. While MRI and CT scans are generally unrevealing, both stroke and intracerebral hemorrhage have been reported in association with CAR T-cell therapy, and MRI can show FLAIR hyperintensity involving the thalami and brainstem.[39] Spine MRI should be considered if there are signs of myelopathy given rare reports of spinal cord edema.[37] Cerebral edema rapidly progressing to brain death in as little as 24 hours has also been reported, with a fulminant case described in CASE 9-3.[38,43,44]

With the increased use of adoptive T-cell therapy, the potential long-term implications of ICANS are now being described. Two reports suggest the presence of long-term neuropsychiatric complications, including cerebrovascular disorders, depression, anxiety, and cognitive difficulty.[45,46] B-cell maturation antigen–targeted CAR T-cell therapy has also been associated with the delayed onset of parkinsonism, with studies showing B-cell maturation antigen expression in basal ganglia neurons and astrocytes.[47] Thus, long-term neurologic surveillance and neuropsychological evaluation should be considered.

Management

The management of ICANS consists of close neurologic monitoring and supportive care. IL-6–directed therapy should be considered for patients with grade 1 or 2 ICANS with concurrent cytokine release syndrome. Dexamethasone 10 mg every 6 hours should be administered in patients with grade 2, 3, or 4 ICANS until there is clinical improvement. The interleukin-1 receptor antagonist anakinra and direct IL-6 antagonist siltuximab are used at some institutions and are actively being studied in clinical trials, although their use in this setting is not approved by the US Food and Drug Administration (FDA).

It is uncertain whether all patients receiving CAR T-cell therapies should be on seizure prophylaxis. Prophylaxis with levetiracetam is often administered for 30 days postinfusion, although some institutions only begin prophylaxis for patients with severe neurotoxicity at high risk for seizures. In one study, seizures occurred in 8% of patients treated with CAR T-cell therapy, but in up to 72% of

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patients with severe neurotoxicity.[39] Nonconvulsive status epilepticus has been reported in as many as 10% of patients and should be managed according to standard practice.[36,48-50] Most patients do not need long-term antiseizure medication as recurrent seizures are rare after the resolution of neurotoxicity.

Monitoring in an intensive care unit should be pursued in all patients with grade 4 ICANS and should be considered in patients with grade 3 ICANS or rapidly worsening neurologic examination. If cerebral edema is highly suspected or seen on imaging, management consists of hyperosmolar therapy, high-dose corticosteroids (methylprednisolone 1000 mg IV daily for 3 days), and other standard treatments for cerebral edema.[36] Intracranial pressure monitoring, CSF diversion, or both should also be considered while weighing the risks of infection and bleeding complications if cytopenias are present. Unfortunately, IL-6–directed therapy is not thought to be effective in this setting. Activation of a CAR T-cell construct's "suicide switch" (triggered by administering an agent that binds to an engineered cell surface component) causing rapid cell ablation or administration of antithymocyte globulin may be considered in severe, life-threatening cases.[37,51] Unfortunately, both approaches also abrogate any antimalignancy effect.

KEY POINTS

- **The mainstay of managing immune effector cell–associated neurotoxicity syndrome (ICANS) consists of high-dose corticosteroids such as dexamethasone. While interleukin-6 directed with tocilizumab may be indicated for cytokine release syndrome, it is generally not effective for the treatment of ICANS.**
- **It remains uncertain whether all patients undergoing chimeric antigen receptor (CAR) T-cell therapy should receive a prophylactic antiseizure medication. Levetiracetam is widely used due to its favorable side effect profile and minimal drug interactions.**

CONCLUSION

With the more widespread use of ICIs and adoptive T-cell therapies, neurologists will need to be increasingly adept at identifying, diagnosing, and managing a wide variety of neurologic complications. The underlying mechanisms of neurologic immune-related adverse events and ICANS remain unclear, leaving room for potentially more effective treatment strategies beyond steroids that do not diminish antitumor efficacy. Additional studies are also needed to identify patients at increased risk of neurologic complications, assess risk in patients with preexisting immune-mediated neurologic conditions, and determine the safety of rechallenge in patients with prior neurologic complications. While early detection and treatment of neurologic complications often lead to favorable outcomes, some neurologic complications may lead to severe neurologic morbidity or death. As immunotherapeutic approaches to treat cancer become more common, neurologists will play an important role in not only acute management but also potentially following patients for chronic neurologic sequelae.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Management of Complications in Neuro-oncology Patients

By Mary R. Welch, MD, MS

ABSTRACT

OBJECTIVE: **The purpose of this article is to familiarize the reader with the spectrum of neurologic and medical complications relevant to the care of patients with neurologic cancer while highlighting best practices to prevent morbidity and mortality. Topics include tumor-related epilepsy, vasogenic edema, complications of corticosteroid use, disruption of the hypothalamic-pituitary axis, venous thromboembolism, and opportunistic infection.**

LATEST DEVELOPMENTS: **In 2021, a joint guideline from the Society for Neuro-Oncology and the European Association of Neuro-Oncology reaffirmed recommendations first established in 2000 that patients with newly diagnosed brain tumors should not be prescribed an antiseizure medication prophylactically. For those with tumor-related epilepsy, monotherapy with a non–enzyme-inducing anticonvulsant is the preferred initial treatment, and levetiracetam remains the preferred first choice. Surveys of physician practice continue to demonstrate excessive use of glucocorticoids in the management of patients with both primary and metastatic central nervous system malignancy. This is particularly concerning among patients who require checkpoint inhibitors as the efficacy of these agents is blunted by concomitant glucocorticoid use, resulting in a reduction in overall survival. Finally, direct oral anticoagulants have been shown to be safe in patients with brain tumors and are now favored as first-line treatment among those who require treatment for venous thromboembolism.**

ESSENTIAL POINTS: **Medical care for patients impacted by primary and secondary central nervous system malignancy is complex and requires a committed team-based approach that routinely calls upon the expertise of physicians across multiple fields. Neurologists have an important role to play and should be familiar with the spectrum of complications impacting these patients as well as the latest recommendations for management.**

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INTRODUCTION

According to the International Agency for Research on Cancer, the global cancer burden is expected to increase by nearly 50% in the next two decades.[1] These projections, coupled with improvements in long-term survival, foretell a parallel rise in late-stage sequelae of cancer and its treatment. Clinicians are thus increasingly likely to

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encounter patients with neurologic cancer in routine practice. The objective of this article is to familiarize the nonspecialist with the spectrum of medical and neurologic complications as well as the latest recommendations in supportive care.

SEIZURES AND ANTISEIZURE MEDICATIONS

First described in 1882 by Hughlings Jackson, tumor-related epilepsy is a common neurologic complication with potentially devastating consequences for patients with intracranial malignancy.[2]

Incidence and Risk Factors

Although patients with secondary or metastatic central nervous system (CNS) cancer outnumber those with primary brain tumors by a factor of 10, they are much less likely to experience seizures.[3,4] According to one study of 2000 patients with intracranial metastases, only 15% experienced this complication.[5] Those with melanoma are more likely to have seizures from metastasis, followed by lung and breast cancers, reflecting the particular affinities of those diseases for the nervous system.[5] In contrast, patients with primary brain tumors are more than twice as likely to experience seizures, although here too histology matters. While rates vary across studies, the inverse association between seizure risk and tumor grade is well described. In one well-cited series of 1028 patients, 49% of patients with glioblastomas experienced a seizure at some point in their disease course, compared to 85% among those with low-grade gliomas.[6] Recent work has suggested that some of the variability may be due to variations in isocitrate dehydrogenase (*IDH*), a recognized hallmark of lower-grade tumors rarely seen in glioblastomas. *IDH*-mutant enzymes result in the accumulation of 2-hydroxyglutarate, a byproduct that is structurally similar to the neuroexcitatory transmitter glutamate and which has been shown in preclinical work to increase the firing rate of cortical neurons, thereby offering a plausible mechanism for heightened seizure risk.[7] In addition, competitive inhibition by excess 2-hydroxyglutarate may suppress the function of α-ketoglutarate, a ketone with demonstrated antiseizure properties.[7,8]

Diagnosis and Workup

Seizures resulting from intracranial malignancy are not always recognized. Most patients impacted by tumor-related epilepsy will have focal seizures with or without altered awareness, and while some will generalize into tonic-clonic events, it is important to educate patients and caregivers to be on the alert for less dramatic presentations such as episodic confusion, behavioral changes, sudden falls, and disorientation on waking. A high index of suspicion is of particular importance among older adults in whom there is a greater risk of incorrectly attributing subtler seizure presentations to delirium, syncope, panic attack, sleep apnea, or even early stages of dementia.[9]

While prevalence is likely under-reported, recent series suggest that about 40% of all patients with glioblastomas experience focal seizures, with up to 25% experiencing both focal and generalized events at some point in their disease course.[4,10,11] Status epilepticus is also not infrequent among patients with brain tumors, with some studies reporting an incidence as high as 10%. Nonconvulsive status epilepticus often presents a diagnostic challenge and should be considered in the appropriate setting. While some patients may present with a prolonged

KEY POINTS

- Given the projected rise in global cancer burden over the next 2 decades, clinicians are increasingly likely to encounter patients with neurologic cancer in routine practice.
- Patients with gliomas whose tumors carry a variation in the isocitrate dehydrogenase gene are at a particularly high risk of seizures, possibly due to the accumulation of 2-hydroxyglutarate, a byproduct of the genetic variant with neuroexcitatory properties.
- Tumor-directed therapies, including the oral chemotherapy agent temozolomide as well as radiation therapy, have been shown to reduce seizure frequency among patients with primary central nervous system malignancy.
- Among patients with low-grade gliomas, consistent use of single-agent temozolomide can allow for the reduction or even discontinuation of antiseizure medications.
- Clinicians should not prescribe antiseizure medications to patients with newly diagnosed brain tumors who have not had a seizure.

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aphasia or neglect syndrome, most cases of nonconvulsive status epilepticus manifest as altered mental status with confusion and lethargy (CASE 10-1). As these symptoms are commonly encountered in advanced stages of disease, the treating clinician needs to maintain a high index of suspicion, but always in the context of overall goals of care.[8,12]

Treatment

The past 3 decades have provided neurologists with an abundance of agents to deploy in the treatment of epilepsy. The goal, however, remains the same: to balance the need for seizure control with both short-term and long-term sequelae of chronic antiseizure medication use. There is no uniform approach and for patients with life-threatening and progressive CNS malignancy, best care requires vigilance, flexibility, and a clear understanding of trade-offs, particularly in late-stage disease.

TUMOR-DIRECTED THERAPIES. Although not as impactful as resection, tumor-directed therapies can reduce seizure frequency. Several retrospective studies have shown that among patients with low-grade gliomas, consistent use of single-agent temozolomide can allow for the reduction or even discontinuation of antiseizure medications, even in the absence of radiographic response. In one such analysis, investigators found a more than 50% reduction in seizure frequency after 6 months in 44% of their sample. Unsurprisingly, given their heightened chemosensitivity, oligodendrogliomas tend to respond better than astrocytomas.[13,14] Based on this and similar studies, seizure control has been proposed as an endpoint for low-grade glioma clinical trials.[15]

While opinions vary about the appropriate use and timing of radiation therapy in patients with low-grade gliomas, it is a standard treatment for those with grade 3 and 4 tumors. During treatment and in the months afterward, ionizing effects may induce an intraparenchymal inflammatory reaction that can result in increased edema and exacerbation of neurologic symptoms including tumor-related epilepsy.[16] However, with temporal distance from radiation therapy (and barring rapid disease progression), patients with both low-grade and high-grade histology can experience a reduction in seizure frequency, a benefit that can accrue irrespective of radiographic response. In one series investigating the impact of radiation therapy, 76% of patients showed a more than 50% seizure reduction, and 38% were seizure-free at 12 months, although none could discontinue antiseizure medications entirely.[17-19]

ANTISEIZURE AGENTS. Despite evidence discouraging the routine use of antiseizure medications as prophylaxis in patients with brain tumors, the practice has remained widespread, prompted in part by the increasing availability of newer drugs with improved safety profiles and fewer drug-drug interactions.[20,21] In a joint Society for Neuro-Oncology and European Association of Neuro-Oncology article, Walbert and colleagues[22] strongly reaffirmed earlier guidelines, citing level A evidence that clinicians should not prescribe antiseizure medications to patients with newly diagnosed brain tumors who have not had a seizure.[22] They further noted that there was insufficient evidence for the practice—still common among over 50% of neurosurgeons—to prescribe these drugs in both the perioperative and postoperative periods.[21] While suggesting that physicians may choose levetiracetam over older antiseizure medications

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CASE 10-1

A 69-year-old man was brought to the hospital after a witnessed generalized seizure. His daughter remarked that he had seemed less communicative in the preceding months. On mental status examination, he struggled with low-frequency words but was otherwise normal. Brain MRI revealed a left frontotemporal fluid-attenuated inversion recovery (FLAIR) hyperintensity with patchy enhancement (FIGURE 10-1). Levetiracetam was initiated and a biopsy yielded a diagnosis of oligodendroglioma, *IDH*-mutant, central nervous system World Health Organization grade 3. While preparing for discharge, staff noticed a marked decline in speech output, prompting continuous EEG and the identification of nonconvulsive status with frequent electrographic seizures. With upward titration of levetiracetam and the addition of lacosamide, the seizures resolved, and his expressive aphasia improved.

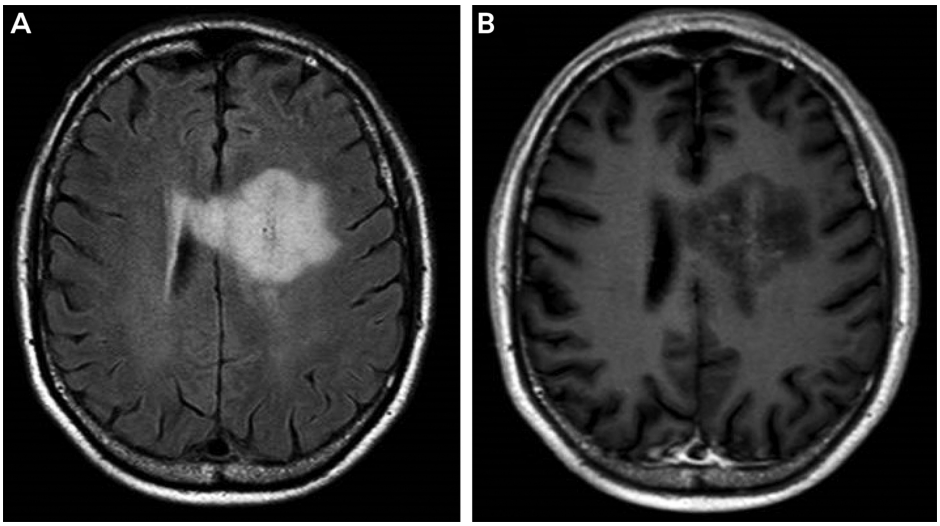

FIGURE 10-1
Imaging of the patient in CASE 10-1. Axial fluid-attenuated inversion recovery (FLAIR) (*A*) and postcontrast T1-weighted (*B*) brain MRI reveal a left frontal lobe mass extending across the body of the corpus callosum with patchy enhancement.

COMMENT

Patients with *IDH*-mutant tumors are at particularly high risk of seizures and, in the absence of motor symptoms, these may go undiagnosed, sometimes for years. Nonconvulsive status epilepticus often presents a diagnostic challenge and consideration of the diagnosis should prompt EEG in the appropriate clinical setting.

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due to its more favorable side-effect profile, there was ultimately insufficient evidence to definitively prefer one agent over another. Notably, they found several small retrospective studies suggesting that the potential antitumor effect of valproic acid and levetiracetam was unconvincing and countered by data from larger pooled analyses. The authors further cautioned that known complications of valproic acid (ie, thrombocytopenia and hepatotoxicity) can potentially lead to dose reductions and delays in actual tumor-directed therapies.[22,23]

CHOICE OF ANTISEIZURE AGENT. Patients with CNS malignancy who do experience a seizure, either partial or generalized, are at high risk of another event and should be on antiseizure medication.[24] When it comes to choosing a specific agent, however, there is no single approach and clinicians must be guided by several considerations including side-effect profile, drug-drug interactions, availability, cost, formulation, speed of titration, and ease of use. Relevant comorbidities should also be taken into account.[4] For instance, lamotrigine might be preferred for patients experiencing severe depression, given its secondary role as a mood stabilizer.[25,26] TABLE 10-1 summarizes key features of antiseizure medications; secondary benefits are noted in the last column.

Several features have made levetiracetam the de facto first choice among neuro-oncologists and neurosurgeons including overall tolerability, lack of drug-drug interactions, affordability, rapid onset, availability in multiple formulations, and ease of titration.[8] Up to 10% of patients taking levetiracetam experience adverse effects—typically fatigue, nervousness, and irritability—that can impact adherence and quality of life.[27] Lacosamide is also frequently prescribed, often as an adjunct or for those patients unable to tolerate levetiracetam.[24] While studies have shown it to be effective and overall well tolerated, its classification as a Schedule V drug in the United States has complicated access for some. Until recently, cost has also been a significant issue and almost certainly curbed its use. However, with the 2022 release of a generic formulation of lacosamide, access and use will likely increase.

CONSEQUENCES AND MANAGEMENT OF VASOGENIC EDEMA

Edema, defined as the abnormal accumulation of fluid within the brain parenchyma, can be characterized as either intracellular or extracellular. The former, known as cytotoxic edema, usually results from ischemic injury such as stroke. The latter is a common feature of intracranial malignancy and occurs in one of two forms.

Hydrocephalic edema, typically described as transependymal flow on imaging, results from the obstruction of CSF and a buildup of hydrostatic pressure that drives CSF from the ventricles into the parenchyma. In contrast, vasogenic edema in patients with neurologic cancer is a direct consequence of blood-brain barrier disruption, either by rapidly dividing malignant cells, the impact of ionizing radiation, or some combination of the two.

Examples of transependymal flow and vasogenic edema are shown in FIGURE 10-2.

Left unchecked, tumor-related edema raises intracranial pressure. This pressure can be diffusely distributed because of hydrocephalus, obstruction of the superior vena cava, or sagittal sinus. More often, it emanates unevenly from a focal lesion, disrupting the neural function of the affected area and producing

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localizing neurologic signs and symptoms. Specific herniation syndromes can also occur as normal brain tissue is pushed into areas of lower pressure.[28–30]

Patients may experience headache mediated by trigeminal pain fibers, nausea with vomiting, and globally depressed consciousness. Vision loss can occur secondary to papilledema, and diplopia from injury to the abducens nerve. Left unchecked, cerebral ischemia ensues as intracranial pressure approaches arterial pressures and the clinical picture evolves into stupor, coma, and death. Long before hospitalization is warranted, however, the vigilant clinician may detect paroxysmal signs and symptoms.[30] Pressure or plateau waves are transient episodes of marked elevation in intracranial pressure, usually lasting minutes.[31] They are thought to result from an increase in blood volume following a sudden decrease in vascular resistance and accompanying vasodilation. Noninvasive monitoring techniques have shown that pressure waves are often asymptomatic, but recognition of the clinical manifestations when they do occur requires a high index of suspicion as they may readily be mistaken for partial seizures or orthostasis. Headache, imbalance, blurred vision, transient confusion, and drop attacks with preserved consciousness are common early manifestations of increased intracranial pressure, although symptoms can be highly variable. Often precipitated by coughing, sneezing, rising from a lying or sitting position, and other movements known to influence intracranial pressure, pressure waves can also occur spontaneously.[30]

Synthetic glucocorticoids are a highly effective first-line treatment for symptomatic vasogenic edema, capable of rapidly ameliorating symptoms and restoring neurologic function. While the precise mechanism of action remains incompletely understood, glucocorticoids appear to exert an antiedema effect by restoration of the blood-brain barrier. For more than 60 years, dexamethasone has remained the most prescribed glucocorticoid among those who treat CNS tumors. While other formulations may be as effective, dexamethasone has no significant mineralocorticoid impact, meaning it is the least likely to cause salt retention and systemic edema. It also has the highest potency relative to other corticosteroids and the longest biologic half-life (>36 hours) which allows for less frequent dosing. Dexamethasone is also less protein-bound, an explanation perhaps for its ability to penetrate the CNS better than other agents.[30]

The optimal dose of steroids for the treatment of tumor-related edema is not firmly established. Vecht and colleagues[32] attempted to address the question in 1994, randomizing 96 patients with brain metastases to one of three dexamethasone doses: 4 mg, 8 mg, or 16 mg daily. They found no differences in terms of impact on neurologic function but did observe substantially higher rates of steroid myopathy 4 weeks into treatment and twice as many cushingoid faces (32% versus 65%) among those who received the highest dose.[32] While acknowledging that the source, distribution, and clinical impact of vasogenic edema can vary significantly across patients, these data nonetheless provide reasonable evidence that 4 mg/d is likely more than sufficient for a majority of patients.[33,34]

UNWANTED EFFECTS OF CORTICOSTEROIDS

Steroids are among the most valuable tools at our disposal. Unfortunately, they also carry a significant risk of side effects, particularly when applied indiscriminately and for prolonged periods.[30] FIGURE 10-3 outlines some of the many toxicities associated with glucocorticoid use. Changes in mood, sleep, and appetite are often among the first side effects to be reported. While some patients

KEY POINTS

- Patients with central nervous system malignancy who experience a seizure, either partial or generalized, are at high risk of another event and should be on antiseizure medication.
- Levetiracetam remains the usual first-choice antiseizure medication for patients with neurologic cancer based on its overall tolerability, lack of drug-drug interactions, affordability, rapid onset, availability in multiple formulations, and ease of titration.
- Up to 10% of patients taking levetiracetam experience adverse effects—typically fatigue, nervousness, and irritability—that can impact adherence and quality of life.
- Vasogenic edema in patients with neurologic cancer is a direct consequence of blood-brain barrier disruption, either by rapidly dividing malignant cells, the impact of ionizing radiation, or some combination of the two.
- Increased intracranial pressure can present with headache, imbalance, blurred vision, transient confusion, and drop attacks with preserved consciousness.
- Synthetic glucocorticoids are a highly effective first-line treatment for symptomatic vasogenic edema, capable of rapidly ameliorating symptoms and restoring neurologic function.

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TABLE 10-1 **Properties of Antiseizure Agents**

Agent	Dosing	Mechanism of action	Metabolism	Half-life and titration
Brivaracetam	3 times daily *OR* 2 times daily extended release (ER)	Synaptic vesicle protein 2A (SV2A) inhibition	Hepatic; substrate of CYP2C19	9 hours
Carbamazepine[a]	3 times daily *OR* 2 times daily extended release (ER)	Sodium-channel blocker	Hepatic; inducer of CY450	16-24 hours, slow titration due to autoinduction
Cenobamate[b]	1 time daily	Sodium-channel blocker, modulates γ-aminobutyric acid A ($GABA_A$)	Hepatic via UGT2B7, CYP2E1, CYP2A6, and CYP2B6	50-60 hours, slow titration
Clobazam[c]	1-2 times daily	Benzodiazepine; $GABA_A$ inhibitor	Hepatic via CYP3A4 (and to a lesser extent CYP2C19)	36-42 hours, slow titration
Gabapentin[d]	3 times daily	Calcium-channel modulator	Renal	Slow titration
Lacosamide[e]	2 times daily	Sodium-channel blocker	Mixed metabolism	13 hours, slow titration
Lamotrigine[f]	2 times daily *OR* 1 time daily ER	Sodium-channel modulator	40% renal; hepatic UGT1A4 coenzyme	14-103 hours, mean 33 hours, very slow titration
Levetiracetam	2 times daily *OR* 1 time daily ER	SV2A inhibition	Unknown; estimated 95% renal clearance	6-8 hours, fast titration
Oxcarbazepine	2 times daily *OR* 1 time daily ER	Sodium-channel blocker	Hepatic; inducer of CYP450	7-11 hours for active metabolite; autoinduction not an issue
Perampanel[g]	1 time daily	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonist	CYP3A4; induces cytochrome P450 at high concentrations	105 hours, slow titration

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Peak plasma	Interactions	Monitoring parameters	Common side effects	Rare but serious side effects
1 hour, 3 hours with high-fat meal		Complete blood count (CBC), renal and liver function	Dizziness, drowsiness, psychiatric disturbances including depression and psychosis	Worsening depression, suicidality, psychosis, leukopenia
Unpredictable, 12 hours, 2 hours as liquid	Can lower chemotherapy concentrations	CBC, renal and liver function, sodium levels, intraocular pressure	Nausea, dizziness, drowsiness, headache, hyponatremia, weight gain, decreased bone density	Aplastic anemia, Stevens-Johnson syndrome, toxic epidermal necrolysis
1-4 hours			Neurocognitive dysfunction, dizziness, incoordination, visual changes	
0.5-4 hours, less for liquid	Metabolizers of CYP2C19 can have 3-5 times concentration		Psychomotor slowing, sedation	
3-3.5 hours			Dizziness, drowsiness, weight gain, peripheral edema	
0.5-4 hours		ECG in patients with conduction or severe cardiac disease	Dizziness	Arrhythmias in patients with conduction problems
2-3 hours	Valproate slows metabolism, reduces efficacy of oral contraceptives	ECG in patients with cardiac history		Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms
1-3 hours			Fatigue, irritability, depression, neurocognitive effects	
Unpredictable, 3-13 hours	Can lower chemotherapy concentrations	Sodium, CBC	Similar to carbamazepine, but more likely to cause hyponatremia	Similar to carbamazepine-aplastic anemia, Stevens-Johnson syndrome, toxic epidermal necrolysis
0.5-2.5 hours	Reduces efficacy of oral contraceptives		Dizziness, irritability, hostility, weight gain	Serious psychiatric and behavioral reactions including aggression, hostility

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Agent	Dosing	Mechanism of action	Metabolism	Half-life and titration
Phenobarbital	1 time daily	Enhances $GABA_A$ receptor	Hepatic; inducer of CYP450	53-118 hours
Phenytoin	2-3 times daily *OR* 1 time daily ER	Sodium-channel blocker	Hepatic (CYP2C > CYP2C19), also inducer of CYP450	6 hours at low concentrations, fast titration
Pregabalin[h]	2-3 times daily *OR* 1 times daily ER	Calcium-channel modulator	Renal	Slow titration
Topiramate[i]	2 times daily, ER available	Multiple sodium-channel blockade, enhanced GABA, AMPA inhibition	Mixed metabolism; weak inducer of CYP450	21 hours, slow titration
Valproate[j]	2 times daily	Enhanced GABA tone	Hepatic; inhibitor of CYP450	8-20 hours, fast titration
Zonisamide	1-2 times daily	Stabilizes neuronal membranes via sodium and calcium channels	Hepatic via CYP3A4	50-68 hours

ECG = electrocardiogram; IM = intramuscular.
[a] Has a secondary benefit as a mood stabilizer.
[b] Take up to 11 weeks to titrate to 200 mcg; not available in generic form or as a liquid.
[c] Controlled substance status that complicates prescribing.
[d] Has secondary benefits of pain and headache relief.
[e] Schedule V classification that complicates prescribing.
[f] Very slow titration due to concern for Stevens-Johnson syndrome; not available as liquid.
[g] Drug reaction with eosinophilia and systemic symptoms.
[h] Schedule V classification that complicates prescribing; has a secondary benefit of pain relief.
[i] Secondary benefits include headache relief and weight loss for some.
[j] Has secondary benefits as a mood stabilizer and for headache relief.

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Peak plasma	Interactions	Monitoring parameters	Common side effects	Rare but serious side effects
8-12 hours	Can lower chemotherapy concentrations	CBC, renal and liver function, phenobarbital	Psychomotor slowing, neurocognitive effects, hypotension	Delayed hypersensitivity including Stevens-Johnson syndrome
2-4 hours with oral, 30 min with IM injection	Dexamethasone	CBC, renal and liver function, trough concentrations for routine monitoring	Fatigue, dizziness, ataxia, blurry vision, gum hyperplasia, irritability	Stevens-Johnson syndrome, blood dyscrasias, lupuslike reaction, hepatitis
3-3.5 hours				
2-3 hours	Reduces efficacy of oral contraceptives		Cognitive dulling, dizziness, kidney stones, weight loss, paresthesia	Hepatic failure, glaucoma
About 2 hours	Slows metabolism of lamotrigine, can increase chemotherapy concentrations	CBC and liver function at baseline and within first 6 months, serum ammonia in case of unexplained lethargy, vomiting or mental status change, serum valproate levels, prothrombin time and partial thromboplastin time prior to any surgery	Gastrointestinal side effects, tremor, insulin resistance, hyperammonemia, psychomotor slowing, neurocognitive effects, hair loss, dyspepsia, thrombocytopenia, dizziness, weight gain	Hepatic toxicity, pancreatitis, polycystic ovarian syndrome, birth defects, severe thrombocytopenia
2-6 hours, less for liquid		Serum bicarbonate prior to initiation and periodically throughout treatment, ammonia if encephalopathy observed	Drowsiness, dizziness, weight loss, kidney stones, apathy	Rash

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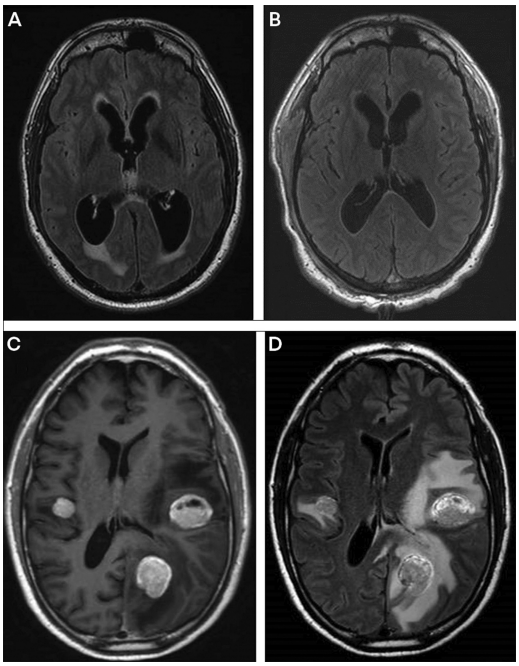

FIGURE 10-2

Examples of different types of cerebral edema. Axial fluid-attenuated inversion recovery (FLAIR) MRI (*A*) hyperintensity radiating outward from enlarged ventricles, an example of transependymal flow, a form of extracellular edema classically seen in patients with hydrocephalus. An axial postoperative FLAIR MRI (*B*) showing interval resolution following third ventriculostomy and resection of an obstructive pineal tumor. Axial postcontrast T1-weighted MRI (*C*) demonstrating enhancing hemorrhagic metastases secondary to melanoma. The vasogenic edema surrounding each mass appears dark on T1-weighted images (*C*) and bright on axial FLAIR images (*D*). The combination of edema and tumor produces mass effect and ventricular compression.

appreciate the added energy they provide, others describe bouts of irritability, heightened anxiety, and emotional lability. Steroids can enhance mood to the point of euphoria, but they can also induce or worsen depression. More severe behavioral disturbances including mania or frank psychosis are thankfully uncommon, but they do occur and must be differentiated from an underlying psychiatric illness or any number of metabolic disorders known to complicate cancer treatment.[35] Sleep (with or without nocturia) is also impacted by steroids and has led many neuro-oncologists to recommend once-daily dosing in the morning. At the very least, patients should be advised to take doses no later than the afternoon to mitigate disruption.[30,33]

Opportunistic Infections

Due to their immunosuppressive properties, glucocorticoids place patients at higher risk of opportunistic infections, particularly when combined with cytotoxic agents such as lomustine (CCNU) or cyclophosphamide (TABLE 10-2).[36]

OROPHARYNGEAL CANDIDIASIS. Oropharyngeal candidiasis is among the most frequently encountered infections.[37] Patients with thrush are frequently asymptomatic and routine inspection is key to diagnosis. Cultures are not required and treatment is initiated on the basis of clinical appearance, regardless of symptomology, as a means of reducing the risk of esophagitis.[30,38] Topical therapy usually suffices, but in more severe cases or among patients unable to cooperate with an oral rinse, systemic treatment with fluconazole produces high cure rates.[30]

***PNEUMOCYSTIS JIROVECII* PNEUMONIA.** *Pneumocystis jirovecii* pneumonia, an opportunistic infection caused by the fungal species *P. jirovecii*, is among the most concerning complications of immunosuppression. While patients with human immunodeficiency virus (HIV) tend to fare better, mortality rates for those with cancer range from 35% to 50%, even with adequate treatment.[39,40] Although the package insert for temozolomide indicates that *P. jirovecii*

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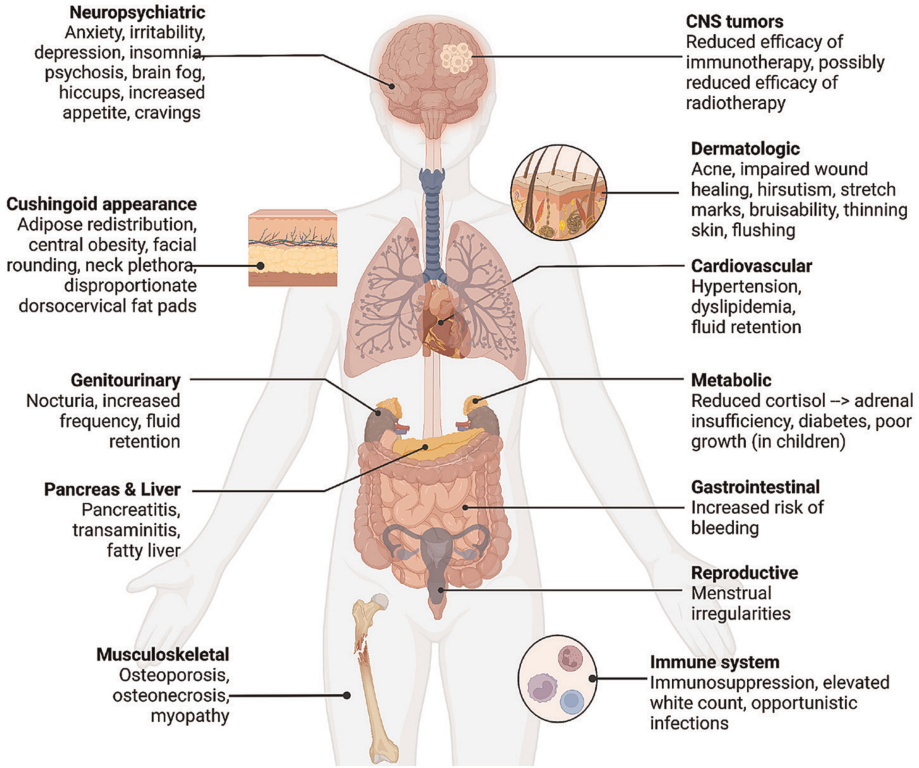
Neuropsychiatric
Anxiety, irritability, depression, insomnia, psychosis, brain fog, hiccups, increased appetite, cravings
CNS tumors
Reduced efficacy of immunotherapy, possibly reduced efficacy of radiotherapy
Dermatologic
Acne, impaired wound healing, hirsutism, stretch marks, bruisability, thinning skin, flushing
Cushingoid appearance
Adipose redistribution, central obesity, facial rounding, neck plethora, disproportionate dorsocervical fat pads
Cardiovascular
Hypertension, dyslipidemia, fluid retention
Genitourinary
Nocturia, increased frequency, fluid retention
Metabolic
Reduced cortisol –> adrenal insufficiency, diabetes, poor growth (in children)
Pancreas & Liver
Pancreatitis, transaminitis, fatty liver
Gastrointestinal
Increased risk of bleeding
Reproductive
Menstrual irregularities
Musculoskeletal
Osteoporosis, osteonecrosis, myopathy
Immune system
Immunosuppression, elevated white count, opportunistic infections

FIGURE 10-3
Adverse effects of glucocorticoids.
Figure created with BioRender.

pneumonia prophylaxis is "required" for all newly diagnosed patients with glioblastoma receiving concomitant radiation therapy, some have challenged the blanket use of this approach and in practice neuro-oncologists often apply the guidelines more selectively, reserving prophylaxis for those whose neurologic symptoms mandate ongoing use of steroids or for those who actually develop lymphopenia on treatment.[41]

Trimethoprim sulfamethoxazole is the most widely used antimicrobial prophylaxis and the recommended first-line agent based on proven efficacy, convenience, and cost. A single double-strength tablet can be given daily or 3 times per week in patients with normal renal function. TABLE 10-3 outlines several alternatives for those with a sulfa allergy or other contraindications to trimethoprim sulfamethoxazole.

Among those not on routine prophylaxis, the diagnosis of *P. jirovecii* pneumonia should be considered in any patient with cancer who is on combined immunosuppressive therapy or has other additional risk factors and reports dyspnea and dry cough.[42,43] Thanks to increased awareness and better screening, clinicians are now more likely to catch the disease in earlier, more moderate stages, but patients may still present in fulminant respiratory failure with dramatic imaging findings (FIGURE 10-4). Although the convenience and rapidity of 1,3-β-d-glucan testing make it a useful adjunct, the assay lacks specificity, and the sensitivity is reduced for patients without HIV or with a low burden of disease.[44] For these reasons, every effort should be made to establish a definitive diagnosis by identification of the organism in either sputum or bronchoalveolar lavage.

KEY POINTS

- For most patients with symptomatic vasogenic edema, 4 mg of dexamethasone per day is more than sufficient; higher doses are rarely warranted.
- Among those not on routine prophylaxis, the diagnosis of *P. jirovecii* pneumonia should be considered in any patient with cancer who is on combined immunosuppressive therapy or has other risk factors and reports dyspnea and dry cough.
- Bevacizumab is a monoclonal antibody that plays an important role in the management of patients with neurologic cancer and symptomatic edema, primarily as a steroid-sparing agent.
- Bevacizumab effectively restores the blood-brain barrier, accounting for its profound antiedema effect as well as the characteristic imaging changes that accompany its use.

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Bevacizumab as an Alternative to Corticosteroids

Given the considerable drawbacks of chronic glucocorticoid use, clinicians have increasingly turned to antiangiogenic agents as an alternative. Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), plays an important role in the management of patients with neurologic cancer, primarily as a powerful steroid-sparing agent.[45,46]

Studies have shown that bevacizumab effectively restores the blood-brain barrier, accounting for its profound antiedema effect as well as the characteristic imaging changes that accompany its use.[47] With the restoration of the blood-brain barrier, gadolinium no longer leaks into the parenchyma to the same extent, and on MRI this apparent resolution of contrast enhancement can easily be misinterpreted as a response to treatment.[33,48] Patients often report symptomatic relief after a single dose and radiographic improvement can be seen in 2 to 3 weeks.[49] Critically, these changes allow for a significant reduction in glucocorticoid use.

As one of only three agents approved by the US Food and Drug Administration (FDA) for the treatment of glioblastoma, nearly all patients with this disease will receive bevacizumab at some point, generally in the recurrent setting where it has been shown to improve quality of life.[50] As illustrated in CASE 10-2, radiation-induced brain injury (ie, radiation necrosis) provides another indication.[51]

TABLE 10-2 Infections Commonly Encountered in Neuro-oncology Practice

Infection	Risk factors particular to patients with neurologic cancer
Dermatologic	
Scalp infection	Tumor-treating field device use, skin changes from chronic steroid use, craniotomy
Decubitus ulcer	Reduced mobility, chronic steroid use, impaired wound healing from bevacizumab
Zoster (shingles)	Immune suppression; patients may require neuropathic pain management
Gastrointestinal	
Hepatitis B	Reactivation by temozolomide
Genitourinary	
Urinary tract infection	Cord compression, urinary retention, catheterization
Neurologic	
Meningitis	Shunt or reservoir placement, intrathecal or intraventricular chemotherapy
Herpes simplex virus encephalitis	Cranial irradiation
Brain abscess, osteomyelitis of skull	Craniotomy
Pulmonary	
Aspiration pneumonia	Altered mental status, cranial neuropathies, reduced mobility
Pneumocystis pneumonia	Chronic steroids in combination with other immunosuppressive drugs

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Corticosteroids and Immunotherapy

In the past decade, immune checkpoint inhibitors, including the anticytotoxic T-lymphocyte–associated antigen 4 agent ipilimumab as well as the anti–programmed cell death 1 and anti–programmed death-ligand 1 drugs, have produced unprecedented improvements in overall survival, revolutionizing the management of a variety of malignancies. Steroids, through their immunosuppressive properties, directly counter the effect of these agents and are the first line in the management of immune-related adverse events.[52-54] In recognition of this, early trials excluded patients with any steroid requirement and subsequent retrospective work has shown their use at the time of immune checkpoint inhibitor treatment corresponds with increased disease progression and mortality. One meta-analysis of 16 studies (N = 4045) found a pooled hazard ratio (HR) for death among patients on steroids of 1.54 (95% confidence interval [CI], 1.24 to 1.91) but noted that the negative impact was concentrated among patients who required steroids for supportive care (HR = 2.5; 95% CI, 1.41 to 4.43) or brain metastases (HR = 1.51; 95% CI, 1.22 to 1.87). In contrast, patients who received glucocorticoids for treatment for immune-related adverse events showed no statistically significant increase in risk of death.[55]

Corticosteroid Dosing and the Importance of Taper

The use of dexamethasone in the management of vasogenic edema for patients with CNS involvement by malignancy should be individualized, clinically based, and judicious. In general, clinical response rather than imaging should guide management, but there may be rational exceptions. Irrespective of indication, continual reassessment is essential, and every attempt should be made to achieve the lowest possible dose necessary to meet the clinical goal.

Dexamethasone 2 mg to 4 mg daily usually suffices for mild to moderate symptoms secondary to vasogenic edema.[32] For patients with more severe

Regimens Used for *Pneumocystis jirovecii* Pneumonia Prophylaxis TABLE 10-3

Options	Dose	Advantages	Disadvantages	Side Effects
Trimethoprim/sulfamethoxazole[a]	480 mg daily or 960 mg 3 times per week	Efficacy, bioavailability, low cost	Short half-life, myelosuppression, multiple drug interactions, hypersensitivity	Fever, rash, headache, nausea and vomiting, myelosuppression, renal dysfunction, anaphylaxis
Aerosolized pentamidine	300 mg inhalation every 4 weeks	Less frequent dosing, better tolerability, effective against other pathogens	Efficacy depends on dispersal, less effective with CD4+ <100 cells/μL, higher cost	Bronchospasm, cough
Atovaquone	1500 mg oral daily	Minimal drug interactions, mild toxicity	Poor bioavailability, higher cost	Fever, rash, headache, nausea and vomiting, diarrhea
Dapsone	100 mg oral daily	Effective against other pathogens	Multiple drug interactions, higher cost	Fever, rash, myelosuppression, methemoglobinemia

[a] Do not use with methotrexate.

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symptoms such as headache with nausea and vomiting, pressure waves, or significant focal neurologic deficit, a common practice is to provide a loading dose of 10 mg followed by an initial maintenance dose of 4 mg twice daily. Many patients notice a benefit within hours, although it typically takes up to 72 hours to see the true impact of any dose change. If there has been no amelioration in symptoms by that time, doubling the dose and reassessing over the next 3 days is an option, although alternate explanations for clinical deterioration should also be considered.[30] Above 16 mg daily, the chances of achieving any meaningful improvement drops while the risk of toxicities goes up.[23,33,56]

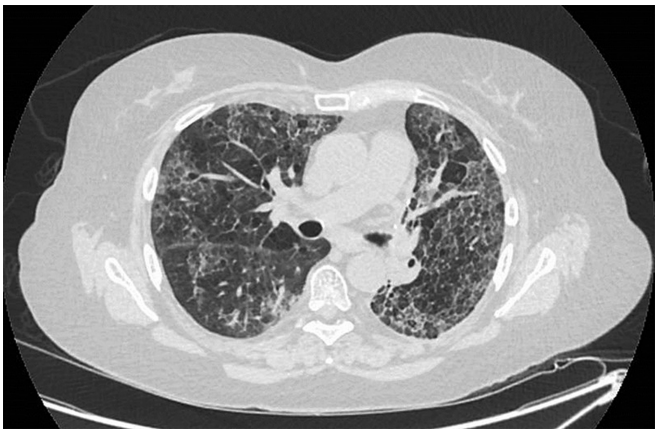

FIGURE 10-4
Pneumocystis jirovecii **pneumonia in a patient with lung cancer metastatic to the brain. Chest CT demonstrates characteristic ground-glass attenuation with interlobular septal thickening.**

Corticosteroid Withdrawal and Hypothalamic-Pituitary-Adrenal Axis Suppression

It is important to counsel patients and caregivers about the possibility of clinical worsening in the setting of steroid reduction. While this may be related to an overly exuberant taper and subsequent undertreatment of vasogenic edema, patients may also experience symptoms of adrenal insufficiency or glucocorticoid withdrawal syndrome (TABLE 10-4).[30] Patients with biochemical adrenal insufficiency may be asymptomatic or they may report multiple complaints that overlap with glucocorticoid withdrawal syndrome, but it is important to distinguish the two as management differs. While adrenal insufficiency requires recalibration of steroids, glucocorticoid withdrawal syndrome symptoms tend to dissipate after each step down in dose and need not provoke an automatic return to a higher dose.[57,58] Adrenal crisis is the most concerning complication of a suppressed hypothalamic-pituitary-adrenal axis. It results when the combination of endogenous cortisol production and exogenous treatment doses proves insufficient to meet the demands of a given stressor (eg, infection, surgery, strenuous exercise). TABLE 10-4 outlines the symptoms.[57,58]

NEUROENDOCRINE AND PITUITARY DYSFUNCTION

Tucked above the cavernous sinus at the intersection of the cortex, cerebellum, and brainstem, the hypothalamic-pituitary axis coordinates much of the body's endocrine system, directly impacting the function of the thyroid, adrenal glands, and gonads while also influencing lactation, water balance, and growth. These structures are often vulnerable to the same insults that damage parenchyma. Direct and indirect forms of compression, the toxic effects of treatment, and

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malignant transformation are all capable of disrupting endocrine function, leading to a wide range of symptoms and substantial impacts on both short-term and long-term health.[59-62]

One cross-sectional study investigated the prevalence, risk factors, and associated adverse health outcomes of hypothalamic-pituitary disorders among childhood cancer survivors. Out of 3141 patients, they found that 40% had deficiencies in growth hormone, 11% lacked sufficient thyroid-stimulating hormone (TSH), another 10% had deficits in reproductive hormones, and 3% had low adrenocorticotropic hormone (ACTH). Not surprisingly, they found significant adverse impacts on bone mineral density, sexual function, weight, cognition, and overall quality of life.[63]

Data on adults who receive irradiation to the hypothalamic-pituitary-adrenal axis are harder to come by, but a 2011 review of 813 patients treated with radiation therapy for nasopharyngeal cancer (N = 608) or intracranial tumors (N = 205) found a point prevalence of 66% (95% CI, 0.55 to 0.76) for any degree of hypopituitarism 2 to 25 years following treatment.[63] These numbers are striking and suggest that many patients experiencing the adverse long-term effects of radiation therapy on their physical, sexual, and neurocognitive health go undiagnosed and untreated.[64] Longitudinal prospective studies are lacking, but the prevalence of hypopituitarism clearly rises with temporal distance from treatment and certain hormones appear to be impacted earlier than others. While statistically significant endocrine changes can occur during the first year of follow-up, they are relatively rare. Taken together, the data suggest that surveillance efforts are currently insufficient and patients would benefit from more rigorous screening in the years following treatment.[59,65,66]

Pituitary reserves may be impacted by any number of factors.[67] One worth highlighting is hypophysitis, which impacts 5% to 17% of patients treated with the anticytotoxic T-lymphocyte–associated antigen 4 agent ipilimumab.[68] Those affected typically present 9 to 12 weeks into therapy with headache and fatigue, although other manifestations of hypothalamic-pituitary suppression including nausea, anorexia, weight loss, and hyponatremia are also seen. More severe clinical manifestations can result from pituitary expansion and compression of surrounding structures as one might see with any growing sellar mass, although visual field deficits are rare.[69] Imaging findings are variable, and up to 25% of cases are undetectable by MRI. More often, there will be slight to moderate enlargement of the pituitary gland with spotty enhancement, T1 hypointensity, and occasional stalk thickening.[69,70] Management generally consists of appropriate hormone replacement, monitoring for signs and symptoms of adrenal crisis, and careful follow-up. Concerns about abrogating the anticancer effects of ipilimumab have generally led to an avoidance of high doses of glucocorticoids except in the most severe cases.[71,72]

VENOUS THROMBOEMBOLISM

A combination of effective prevention strategies as well as advances in the management of venous thromboembolism (VTE) have led to significant improvements in outcomes.[73] In particular, the development and application of direct oral anticoagulants have simplified treatment and improved patient quality of life. However, with a 10% inpatient mortality rate, acute pulmonary

KEY POINTS

- Excessive use of glucocorticoids can have a negative impact on overall survival, particularly among patients treated with checkpoint inhibitors.
- The use of steroids in the management of vasogenic edema for patients with central nervous system malignancy should be individualized, clinically based, and judicious.
- It is important to counsel patients and caregivers about the possibility of clinical worsening in the setting of steroid dose reduction.
- Hypophysitis impacts 5% to 17% of patients treated with the anticytotoxic T-lymphocyte–associated antigen 4 agent ipilimumab.

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CASE 10-2

A 62-year-old woman was brought to the hospital by her daughter after several falls and 2 months of behavioral changes. Eighteen months prior to presentation, she had undergone subtotal resection of a large bifrontal olfactory groove meningioma followed by 54 Gy of radiation, delivered over 28 fractions. Brain MRI (FIGURE 10-5A and 10-5B) revealed periventricular enhancement with associated fluid-attenuated inversion recovery (FLAIR) hyperintensity concerning for vasogenic edema, all within the prior treatment field. She was treated with a course of dexamethasone for presumed radiation necrosis, but this had little impact on her imaging and exacerbated her long-standing brittle diabetes. She was started on bevacizumab infusions and, after three doses, had near complete resolution of all enhancement as well as a substantial reduction in her edema (FIGURE 10-5C and 10-5D). Her symptoms also improved, although several years later she had to transition to assisted living for presumed radiation-induced dementia.

COMMENT

While bevacizumab has proved disappointing in the treatment of high-grade gliomas, its ability to restore the blood-brain barrier and function as a steroid-sparing agent can result in significant improvements in patient function and overall quality of life.

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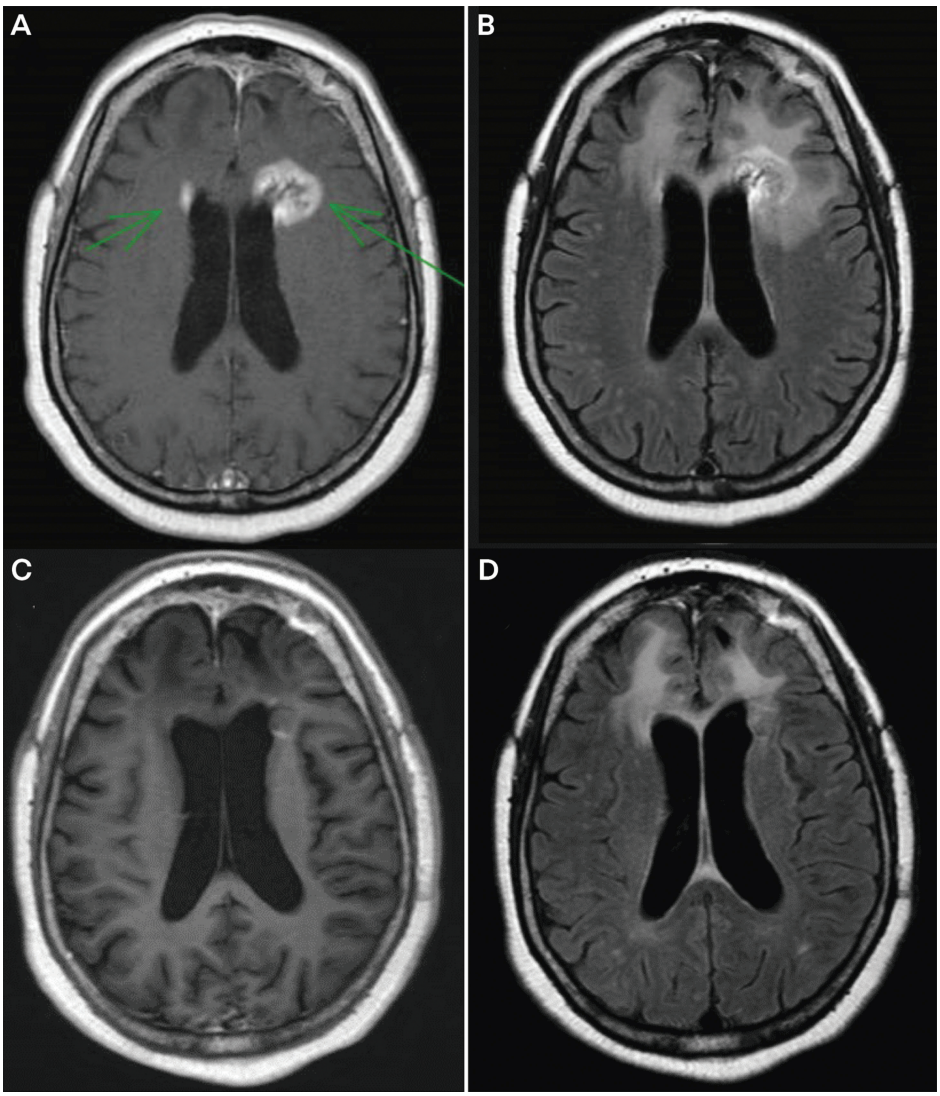

FIGURE 10-5

Imaging of the patient in CASE 10-2 showing radiation necrosis and treatment response to bevacizumab. *A*, Axial T1-weighted postgadolinium contrast sequence shows enhancing disease adjacent to the lateral ventricles (*arrows*), an area with known vulnerability to the toxic effects of radiation. *B*, Associated axial fluid-attenuated inversion recovery (FLAIR) hyperintensity, which reflects a combination of vasogenic edema and more chronic demyelinating changes from treatment. *C*, Axial T1-weighted postgadolinium contrast sequence showing near-complete resolution of enhancement following three doses of bevacizumab. *D*, Axial FLAIR sequence demonstrating corresponding reduction in vasogenic edema; the hyperintensity that remains is indicative of more long-standing postradiation white matter change.

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TABLE 10-4

Complications of Steroid Withdrawal

Adrenal insufficiency

- Abdominal cramping
- Diarrhea
- Dizziness
- Fatigue
- General malaise
- Hair thinning
- Hypoglycemia (more often in children and patients with diabetes)
- Hyponatremia
- Hypotension and orthostasis
- Light-headedness
- Low libido
- Low mood
- Mental fog and poor concentration
- Nausea, vomiting
- Pallor
- Poor weight gain and growth in children

Withdrawal syndrome

- Fatigue
- Headaches
- Irritability
- Joint pain
- Lightheadedness
- Loss of appetite
- Muscle or body aches
- Nausea

Adrenal crisis

- Altered mental status
- Eosinophilia
- Fever
- Hypoglycemia
- Hyponatremia
- Hypotension or hypovolemic shock
- Lymphocytosis
- Nausea or vomiting
- Seizures
- Severe fatigue

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embolism remains a significant threat to patients with cancer, and vigilance for signs and symptoms of VTE is essential.[74,75]

Epidemiology and Risk Factors

VTE, including deep vein thrombosis (DVT) and pulmonary embolism, is common among patients with cancer and a significant cause of morbidity and mortality. Incidence varies widely depending on the sample population, ascertainment method, and extent of follow-up, but some studies have estimated that upwards of 10% of patients with cancer experience symptomatic VTE at some point in their disease course.[76,77] Tumor type, location, the extent of disease, patient comorbidities, and certain medications influence VTE risk (TABLE 10-5). According to several studies, the incidence of VTE among patients with cancer is on the rise, possibly due to improved survival, novel cancer therapies, and improved detection.[74] A Danish cohort study compared nearly 500,000 patients with cancer with age-matched controls and observed a threefold increase in the incidence of VTE among the patients with cancer and a sixfold increase in those using chemotherapy or targeted therapy.

Patients with primary CNS malignancy are at particularly high risk of VTE.[78] Estimates vary, but some studies suggest that up to one-third of patients are affected.[79,80] As with the larger cancer population, the risk is heightened at the time of diagnosis, possibly related to surgery and associated immobility, but it remains elevated throughout the disease course, particularly among patients whose neurologic deficits include paresis.[81,82] Grade matters: high-grade gliomas account for the vast majority of VTE among patients with brain tumors and recent work has found that the absence of an *IDH1* variation, a defining molecular feature based on the latest WHO criteria, is associated with a threefold increase in VTE risk when compared to patients with *IDH* variations.[80,83]

No Role for Prophylaxis

Given the high rates of VTE among patients with gliomas, the PRODIGE study was conducted to determine the efficacy and safety of prophylaxis in this population. Patients with newly diagnosed malignant gliomas were randomized to dalteparin 5000 IU (anti–factor Xa) or placebo for 6 months for the prevention of VTE. Although the study was terminated early, preliminary data suggested a trend toward a reduction in VTE incidence in the treatment arm (11% and 17%, low-molecular-weight heparin group versus placebo, $P = 0.3$). However, a disconcertingly high rate of intracranial hemorrhage (5.1% and 1.2%, low-molecular-weight heparin versus placebo, $P = 0.2$) was also observed, curbing enthusiasm for the approach.[84]

In the absence of any clear role for prophylaxis, clinical vigilance as well as patient and caregiver education remain the best means to mitigate risk. Patients should be routinely screened for known risk factors and educated about the signs and symptoms to watch for including unilateral leg swelling with or without tenderness and erythema, palpitations, pleuritic chest pain, dyspnea, and cough. New-onset tachycardia or low values on pulse oximetry in the setting of these examination findings should prompt workup with chest CT angiography.

Treatment with Direct Oral Anticoagulants

In the past, heightened concerns over intracranial hemorrhage resulted in an overreliance on inferior vena cava filters and overall hesitation to treat, but more

KEY POINTS

- Patients with primary central nervous system malignancy are at particularly high risk of venous thromboembolism, with some studies suggesting that up to one-third of patients are affected.
- Direct oral anticoagulants have been shown to be safe in patients with brain tumors and are now favored as a first-line treatment among patients who require treatment for venous thromboembolism.
- Inferior vena cava filters should only be deployed in patients who have strict contraindications to anticoagulation and life-threatening thrombus burden.

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recent work has demonstrated the relative safety of direct oral anticoagulants in patients with both primary and metastatic brain disease.[85] Several retrospective studies offer compelling evidence that they are not only the most convenient choice for patients, requiring neither routine monitoring nor subcutaneous injections, but are also the safest and most effective choice. Importantly, direct oral anticoagulants do not appear to confer an increased risk of intracranial hemorrhage.[85-87] For this reason, most neuro-oncologists align themselves with VTE guidelines established by the American Society of Clinical Oncology and recommend direct oral anticoagulants rather than low-molecular-weight heparin or warfarin for the outpatient management of VTE.[88] TABLE 10-6 summarizes the options.

Anticoagulation remains the cornerstone of treatment for any VTE, but judgment is required to safely balance the risks of hemorrhage versus thrombosis. Strict contraindications include evidence of an enlarging, clinically significant intracranial hemorrhage, uncontrolled malignant hypertension,

TABLE 10-5 **Risk Factors for Venous Thromboembolism In Patients With Cancer**

Across all patients with cancer

- **Disease-related**
  - Cancer stage, presence of metastases
  - Cancer type: brain, colorectal, lung, ovaries, pancreas, stomach
  - Genetic variants (eg, *ALK* variation in lung cancer)
  - Time relative to diagnosis; increased within first year
  - Tumor grade
- **Patient-related**
  - ABO blood type
  - Acute illness
  - COVID-19
  - Elevated platelet count (≥350,000/μL)
  - Family history of venous thromboembolism (VTE)
  - Hereditary thrombophilia
  - History of VTE
  - Increased prothrombin time
  - Leukocytosis
  - Long-standing comorbidities: heart failure, hypertension, respiratory disease
  - Obesity
  - Older age
  - Tobacco use

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severe coagulopathy, platelet dysfunction, or thrombocytopenia (defined as a platelet count of less than 50,000).[88]

Relative contraindications should be based on a thoughtful assessment of bleeding risk prior to anticoagulation. Metastases secondary to melanoma, choriocarcinoma, and thyroid and renal cell carcinomas have a known propensity to bleed and will likely give pause, but as long as there is no evidence of acute bleeding on imaging, it is likely reasonable to proceed.[89] Retrospective work provides some reassurance for this approach; one well-designed 2012 case control study compared 57 patients with intracranial melanoma treated with enoxaparin for VTE to matched controls and found no meaningful differences in rates of intracranial hemorrhage.[90]

While randomized studies have demonstrated good efficacy in the prevention of pulmonary embolism, inferior vena cava filters have not been shown to impact overall survival. Moreover, their high complication rate and tendency to paradoxically increase clot burden in the leg can substantially impact patient

CONTINUED FROM PAGE 1864

- **Treatment-related**
  - Chemotherapy: asparaginase, cisplatin
  - Combination lenalidomide and high-dose dexamethasone
  - Erythropoiesis-stimulating agents
  - Hormonal therapy: tamoxifen, raloxifene
  - Immunotherapy and chimeric antigen receptor T-cell therapy
  - Presence of indwelling catheter or port
  - Radiation therapy
  - Surgery
  - Targeted therapy: CDK4/CDK6 inhibitors, antiangiogenic agents

Brain tumor specific

- **Disease-related**
  - Limb paresis, immobility
  - Podoplanin expression
  - Tumor grade
  - Tumor size
  - Wildtype *IDH*
- **Treatment-related**
  - Bevacizumab use
  - Low platelets
  - Operative time >4 hours

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quality of life. For these reasons, filters should only be deployed in patients with strict contraindications to anticoagulation and a life-threatening thrombus burden.[89]

The appropriate duration of anticoagulation remains an unanswered question in oncology. For patients with active malignancy and a first episode of VTE, a course of 3 to 6 months is typically recommended. Afterward, patients with benign or indolent tumors can usually discontinue treatment with careful follow-up and attention to symptoms. However, among those with active malignancy in whom the prognosis is more guarded, long-term or even lifelong therapy is generally warranted.[89,91]

TABLE 10-6 **Anticoagulants Used In the Treatment of Venous Thromboembolism[a,b]**

Anticoagulant	Treatment dosing	Factors to consider	Reversal agent
Factor Xa inhibitors			
Rivaroxaban	15 mg 2 times daily with food for 21 days, then 20 mg 1 time daily with food	No initial parenteral therapy required; once-daily dosing	Andexanet alfa
Apixaban	10 mg 2 times daily for 7 days, then 5 mg 2 times daily	No initial parenteral therapy required	Andexanet alfa
Edoxaban	Parenteral anticoagulation for 5 days, then edoxaban 60 mg 1 time daily	Requires initial parental therapy; once-daily dosing	Andexanet alfa
Direct thrombin inhibitor			
Dabigatran	Parenteral anticoagulation for 5 days, then dabigatran 150 mg 2 times daily	Requires initial parental therapy; avoid in patients with coronary artery disease	Idarucizumab
Vitamin K antagonist			
Warfarin	5 mg 1 time daily for most patients, target international normalized ratio range of 2-3	Affordable, but less convenient; requires monitoring with labs; use in patients with severe renal disease (creatinine clearance <30 mL/min)	Vitamin K, fresh frozen plasma, prothrombin complex concentrates
Low-molecular-weight heparin			
Dalteparin	100 mg units/kg 1 time daily or 100 units/kg every 12 hours	For use in pregnancy or in case of coagulopathy or liver disease; use fondaparinux in cases of heparin-induced thrombocytopenia	Andexanet alfa, protamine
Enoxaparin	1 mg subcutaneous every 12 hours or 1.5 units/kg 1 time daily	Same considerations as dalteparin	Andexanet alfa, protamine

[a] For elective procedures with high bleeding risk, including craniotomy, give last dose of direct oral anticoagulant 3 days prior to surgery; resume 48 hours after; adjust in cases of poor renal function.
[b] Avoid concomitant antiplatelet therapy if feasible due to increased bleeding risk.

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CONCLUSION

Continuum's last neuro-oncology issue was published in 2020. What has changed since then? The approach to tumor-related epilepsy and neuroendocrine disruption has undergone some refinements, but many of the management principles remain unaltered. In contrast, attitudes toward steroid use appear to be shifting, albeit slowly. In the face of accumulating data demonstrating their negative impact on both short-term and long-term health outcomes, specialists in neuro-oncology have, for some time, emphasized the need to minimize exposure to glucocorticoids. This has led to more temperate dosing, an emphasis on treating symptoms rather than scans, frequent reassessment of steroid need, and increased likelihood of taper. Despite education efforts, the habit of blanket "4 mg Q4" dosing persists, although there are signs that the message is getting through. The increased use of immunotherapy with its mandated limits on glucocorticoid use has also likely had an impact.

Finally, new evidence on the safety of direct oral anticoagulants in the treatment of cancer-related VTE has fundamentally changed the approach to anticoagulation in the past 2 years, even among patients with CNS disease. In addition to sparing patients the inconvenience of twice-daily injections, findings now suggest that these agents are associated with a lower risk of intracranial hemorrhage compared with low-molecular-weight heparin. As a result, direct oral anticoagulants are now favored as a first-line treatment among patients with both primary and metastatic brain tumors who require treatment with VTE.

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CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Palliative Care and Care Partner Support in Neuro-oncology

By Akanksha Sharma, MD

ABSTRACT

The journey for a patient with a brain tumor and their loved ones can be extremely challenging due to the high burden of physical symptoms and the emotional distress caused by the diagnosis. Optimizing quality of life by addressing symptoms and reducing this emotional distress can improve treatment tolerance and outcomes and alleviate care partner distress and burden. Symptoms in patients with central nervous system (CNS) tumors can vary in onset and intensity, ranging from headaches, seizures, and focal weakness to emotional distress and cognitive dysfunction. Additionally, care partners may demonstrate distress due to the high burden of care and need appropriate support structures and access to resources to alleviate this stress. Evidence-based recommendations are unfortunately limited given the lack of high-quality research in this area, but patients living with CNS tumors and their loved ones can benefit from early and routine symptom identification and management, compassionate and transparent communication, and practical guidance for the future. These principles are part of palliative care, a field of medicine focused on alleviating suffering in patients with serious, chronic illness. Clinicians involved in the care of patients with CNS tumors must be educated in these important primary palliative care principles. This article focuses on key symptom management, strategies for high-quality communication, a discussion of advance care planning, and an overview of end-of-life care.

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RELATIONSHIP DISCLOSURE:
Dr Sharma has received personal compensation in the range of $0 to $499 for serving as a speaker with Project Ronin, and in the range of $500 to $4999 for serving on an advisory board with the National Brain Tumor Society and on a scientific advisory or data safety monitoring board for Novocure. The institution of Dr Sharma has received research support from Apollomics, Inc., Chimerix, Incyte, and Novocure.

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Dr Sharma reports no disclosure.

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INTRODUCTION

Palliative care is a person-centered approach that focuses on improving the quality of life of patients and care partners suffering from the broad-reaching impact of serious illness. The simplest definition describes palliative care as a specialty that focuses on identifying and addressing suffering in all its forms, including physical, psychological, emotional, social, and spiritual. This is done via a dedicated focus on certain pillars or principles of care: symptom management, care coordination, goals of care clarification and advance care planning, high-quality communication, and support for the patient's loved ones. Palliative care is appropriate and warranted at any stage in a patient's journey with serious illness, from diagnosis onward. It should not be confused with hospice, which incorporates palliative care principles into the care of patients who are at or nearing the end of life.

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A 2010 trial demonstrated the benefit of palliative care integration into oncologic care for patients with advanced metastatic cancer, showing a significant benefit to quality of life and survival.[1] Since then, the field has grown in many countries, including the United States, Canada, Australia, and the United Kingdom, with extensive literature now demonstrating the benefit of integrating palliative care into the care of patients with various types of serious illness ranging from cancer and amyotrophic lateral sclerosis to severe congestive heart failure. Within both oncology and neurology, there has been a push in recent years to recognize the high unmet need of patients when it comes to suffering, and the potential of palliative care in closing this gap. Guidelines for oncologic care now explicitly state the need for early integration of palliative care into the care of any patient being treated for cancer, where available.[2,3] Given the limited availability of such specialists and teams, these guidelines also address the need for increased clinician education on the principles of palliative care so that it may become a part of routine care. In 2022, the American Academy of Neurology (AAN) released an updated position statement on the integration of palliative care into neurology.[4] In 2021, the International NeuroPalliative Care Society was formally launched to promote the integration of palliative care within neurology.[5]

Patients with central nervous system (CNS) tumors straddle the worlds of neurology and oncology, coping with tumors that can cause significant physical and emotional distress, as evidenced by the high burden of disease and treatment-related symptoms identified in the literature.[6] Apart from the burden of neurologic symptoms, they also often cope with the impact of oncologic treatments such as surgery, radiation, and a range of toxic but necessary systemic therapies. Patients living with such complex, devasting diagnoses benefit greatly when their primary clinical teams incorporate palliative care principles into their care, though they may also need additional support from clinicians specialized in palliative medicine when available and appropriate. It should be noted that not all aspects of palliative care as presented here are universally accepted; there must be considerations based on cultural, religious, ethnic, and geographic variations across communities. In the author's experience, these variations are best addressed by practicing culturally competent care, which begins by seeking permission, exploring information preferences, and respecting boundaries set by the patient and loved ones.

THE IMPORTANCE OF CARE PARTNERS

The term *care partner* is used in this article to describe any loved one who is heavily involved in the patient's day-to-day care or decision making. The care of a patient with a brain tumor cannot be limited to the individual alone. The impact of such a diagnosis is profound, affecting relationships and the patient's loved ones. Indeed, the absence or loss of care partners has a direct impact on quality of life in patients with brain tumors given their high needs and early dependence.[7] It is therefore crucial to consider care-partner well-being as part of a patient's overall care plan.

It is natural and expected that care partners will experience a myriad of emotions soon after diagnosis (eg, shock, anger, resentment, guilt, fear, grief), but the focus remains understandably on the patient. It may be difficult for care partners to find an outlet for their concerns, fears, and disappointment. The clinical team should communicate with care partners early on and encourage them to seek help in the form of therapy, counseling, or support groups, where they may find community and build coping strategies. Actively engaging care partners throughout the

KEY POINTS

- **Palliative care, a person-centered approach that aims to alleviate suffering and improve the quality of life of patients with serious illness and their care partners, should be an integral part of care for patients with central nervous system (CNS) tumors.**
- **Care partners of patients with CNS tumors carry a high burden and may be impacted emotionally, physically, socially, and financially. They benefit from being actively engaged by the care team, receiving education and support, and being directed to resources as and when needed.**
- **Headaches in patients with CNS tumors can have many contributing factors and a careful history is needed to help develop the most appropriate plan of care.**

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patient's illness, providing them with education and information, and preparing them to manage the patient's symptoms can be helpful interventions. A model that specifically delivers support at predetermined transition times in the form of education, needs assessment, communication, and care-partner engagement has been developed.[8] This model was found to be feasible and acceptable, and should be considered by care centers involved in CNS tumor care.[8] In the following sections, care-partner-specific considerations are discussed where appropriate.

SELECTED SYMPTOMS AND THEIR MANAGEMENT

This section discusses many of the symptoms commonly experienced by patients with brain tumors and provides some guidance on their management.

Headache

Patients with CNS tumors can have headaches due to a variety of causes, such as intracranial pressure from mass effect or vasogenic edema, leptomeningeal inflammation from disease, fatigue, sleep disturbance, medication side effects, dehydration, cervical or occipital neuralgia, overuse of short-acting drugs, anxiety and stress, and migraine.[9] Edema or mass effect may need to be addressed with steroids (generally dexamethasone due to its high potency and long half-life) or by addressing the root cause (such as craniectomy to debulk the tumor). Dexamethasone should only be used judiciously and for a limited period, given the side effects associated with prolonged use (eg, immunosuppression, peripheral edema, diabetes, weight gain, myopathy, adrenal insufficiency, skin breakdown).[10] When headaches are due to edema and steroids are not effective or must be weaned, bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, may be helpful as a steroid-sparing agent for certain tumor types.[11]

Overall, the successful management of headaches requires a careful review of the features and location of the headache and any exacerbating and alleviating factors, and evaluating the patient's medications, sleep quality, and other comorbidities.[12] Unfortunately, there have been no specific studies looking at prophylactic agents in this patient population; thus, management is extrapolated from the general headache population, where oral preventative medications include the classes of beta-blockers, angiotensin receptor blockers, antiseizure drugs, and antidepressants.[13] Nonsteroidal anti-inflammatory drugs and acetaminophen may be a mainstay for abortive therapy, but the risk of intracranial hemorrhage, overuse syndrome, or rebound headache should be considered. For headaches with migraine features, the newer class of calcitonin gene-related peptide receptor antagonists are increasingly used with anecdotally good effect, although these have not been formally studied in patients with brain tumors. In cases of neoplastic meningitis or cerebral edema where steroids are ineffective despite titration, opioids may be necessary and can be helpful, but it may be prudent to involve a pain management or palliative care consultant as proper dosing and the use of specific agents (eg, methadone) may require specific training and experience. Strategies that lack evidence but may be helpful and low risk include mindfulness or meditation techniques, integrating melatonin and magnesium supplements, and using massage, trigger-point injections, and acupuncture therapy.

Emotional Distress and Psychiatric Symptoms

A diagnosis of a CNS tumor is overwhelming and distressing. Surgery, radiation therapy, chemotherapy, and the repeated sequence of imaging scans

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every few months contributes further to the anxiety and stress of the disease process. Even with definitive surgery, the fear of recurrence or growth often persists. Patients with CNS tumors and their care partners have a high burden of anxiety, depression, posttraumatic stress disorder, and existential distress.[14-16] The psychological distress may translate into poorer tolerance of treatment and reduced quality of life. Despite the recognition of the downstream impact of these symptoms, there has been little research in this area.[17]

In the author's experience, it is best to follow a multipronged approach when possible, which may include a trial of a medication (chosen based on medical history, interactions, and side effects) and referral to psychological counseling, preferably with a therapist experienced with serious illness. No single model of therapy has been identified to improve outcomes in patients with cancer (though this may be more a reflection of the study designs and outcomes chosen for evaluation), but individualized therapy has shown benefits in the management of anxiety, depression, and stress.[18-20]

Psychologic support may be available through social workers, licensed marriage and family therapists, psychologists, or psychiatrists at the patient's medical center or within the community. It should be noted that counseling or therapy is not a universally accepted modality of treatment due to existing taboos and a strong distrust in many cultures. Even when culturally accepted, counseling may be hard to find or difficult to afford, though increasingly online portals and even the use of artificial intelligence are used to meet this growing need. Mindfulness-based stress reduction programs and meditation practices have demonstrated benefit for mood, sleep, and fatigue in patients with cancer and in smaller interventions with patients with brain tumors.[21-23] Peer support may be helpful for both patients and care partners, through either a disease-specific support group or social media. These groups can help normalize the experience and provide a sense of community to combat the isolation that may be experienced with rare brain tumors.[24-26] As the patient declines cognitively and physically, care partners can also become increasingly anxious, depressed, and fearful of the future; it is important to identify these at-risk care partners and ensure they have access to resources such as respite care, therapy, support groups, financial counseling, and paid aides.[27,28]

Existential distress can include a sense of hopelessness, demoralization, a loss of personal meaning and dignity, feeling like a burden or a cause of distress to others, and discomfort with living or loss of will to live.[29] In the setting of serious illness, existential distress may often coexist with death anxiety—the fear of death and dying—a dichotomy that itself leads to additional emotional distress.[30] Both have been described in patients with brain tumors and their care partners.[31-35] These are challenging symptoms to treat in the seriously or terminally ill. Psychological interventions, especially meaning-centered psychotherapy and dignity therapy, have been noted to be effective and should be explored as an option through referrals to appropriate specialists in psychology, psychiatry, or palliative care.[36-38] Meaning-centered psychotherapy, inspired by the work and writings of Victor Frankl, is a structured psychotherapeutic intervention that aims to help patients and care partners suffering from despair due to a loss of meaning triggered by serious illness. There is an established paradigm that has demonstrated benefit in a randomized controlled trial in patients with existential distress, and it is also

KEY POINTS

- **Dexamethasone should only be used when the headache is attributed to edema or mass effect, and to avoid toxicity it should be used at the lowest required dose for the shortest possible amount of time.**
- **Patients with CNS tumors and their care partners report a high burden of anxiety and distress which can severely impact quality of life, but this area remains under-researched and management is extrapolated from the general population of patients with cancer.**

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being evaluated in care partners of patients with cancer (notably with a pilot study in care partners of patients with glioblastoma).[36,38]

Dignity therapy aims to address distress in patients who are terminally ill or nearing death through a structured intervention designed to develop meaning and purpose by exploring topics that matter most at this phase of their life and how they hope to be remembered.[39] In patients with cancer, benefit has been noted in the sense of well-being and quality of life.[40] Psychedelic-assisted psychotherapy utilizes psychedelic compounds that can modify consciousness temporarily as an adjunct to therapy for patients seeking relief from anxiety, distress, posttraumatic distress, existential distress, and death anxiety. It is increasingly being explored as a viable treatment option for those with advanced cancer and their care partners, with early studies showing promise and durable response rates. A limited number of doses may be embedded into a course of psychotherapy with preparatory and integrative counseling sessions built in to prepare for and debrief from the experience. This could be a future option for patients with CNS tumors if efficacy is established and safety is demonstrated.[41-44]

Patients with CNS tumors can have a variety of neuropsychiatric manifestations regardless of tumor location, ranging from disinhibition, apathy, and anhedonia to hallucinations, agitation, personality changes, and irritability.[45,46] Medications such as dexamethasone or levetiracetam can further exacerbate these symptoms, as can sleep deprivation, underlying anxiety, and seizures. Management of these symptoms can be quite challenging, especially when present at the time of diagnosis, as patients may lack insight into their behavior, adding to the distress experienced by care partners.[47] No evidence-based guidelines exist for the management of these symptoms; there is a need for an evidence base to inform recommendations for psychosocial support.[48] Input from an experienced psychiatrist or psychologist, such as a psycho-oncologist, may be invaluable. Depending on the severity of symptoms, medications such as olanzapine, quetiapine, risperidone, or benzodiazepines may be needed, but side-effect profiles, cardiac risks, and risks of lowering the seizure threshold should be considered. Valproic acid, oxcarbazepine, and lamotrigine may be helpful in patients with emotional lability or disinhibition, but drug interactions and risk of rash must be carefully considered.

It is important to support care partners who may be on the receiving end of these behaviors by actively inquiring about symptoms and challenges at home, educating them about the underlying causes, helping them troubleshoot difficult situations, and normalizing reactions or emotions. Education on why these behaviors occur (and how they are usually not under the patient's control) can be surprisingly empowering and reassuring, as care partners may be taking responsibility for and experiencing guilt or anger over the situation. Care partners should be encouraged to seek therapy or counseling, take regular breaks, and plan for respite. It is important to ensure that patients are not dangerous to themselves or their loved ones. In these situations, suicidal or homicidal risk should be assessed, loved ones should be queried about the presence of guns in the home, and a safety plan should be developed in case the patient experiences a severe behavioral outburst. In some cases, it may be in everyone's best interest for the patient to be transitioned to a memory care or other facility where experienced care can be provided. These decisions are extremely difficult and may be traumatic, and care partners need the support of their medical teams and social work services when navigating them.

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Sleep Disorders

Sleep-wake disturbances in patients with CNS tumors can result in difficulty falling or staying asleep (insomnia), poor quality of sleep, and excessive daytime somnolence. One study identified that 61% of patients with primary brain tumors reported poor sleep quality and 21% experienced insomnia.[49] These disturbances in turn can significantly impact daily living, quality of life, and both emotional and physical health.[50]

A myriad of factors may be responsible for sleep-wake disturbances in these patients, ranging from endocrine dysfunction, medication side effects, and hypothalamic dysfunction to pain, anxiety, and psychosocial stressors.[51] Again, studies evaluating mechanisms or assessing interventions remain very limited in this population; a 2017 review highlighted that there were only 13 studies between 2000 and 2016 that evaluated sleep-wake disturbances in patients with brain tumors.[52] This same review discussed a stepwise assessment for sleep-wake disturbances that can be very helpful as a practical guide for evaluating these patients. If sleep difficulties are identified, the next step is to consider a sleep disorder (eg, sleep apnea, restless legs syndrome, narcolepsy) and referral to a sleep specialist. The last step is to evaluate the many factors that can contribute to sleep difficulties and address each in a stepwise manner, starting from reviewing medications (including dosing and schedule) to considering referrals for the management of comorbid psychiatric conditions.[52]

Among nonpharmacologic treatments for sleep disorders in patients with cancer, cognitive behavioral therapy for insomnia, mindfulness-based stress reduction, and exercise have the most evidence.[52] Cognitive behavioral therapy for insomnia has demonstrated great benefit through encouraging behavior changes that allow for restricting daytime sleep, improving sleep hygiene, and controlling exposure to stimuli.[53] Mindfulness-based stress reduction and exercise both help with overall health and well-being (when the patient is physically able to participate) and have demonstrated benefit in improving sleep quality and reducing fatigue in patients with cancer (though studies in patients with brain tumors are lacking).[54,55]

Pharmacologic agents used to alleviate sleep symptoms range from over-the-counter medications such as melatonin, magnesium, and antihistamines to benzodiazepine or nonbenzodiazepine hypnotics, and antidepressants such as doxepin or trazodone.[51] There are no trial data assessing the efficacy or safety of these agents in patients with brain tumors. These drugs may have a hangover effect, contribute to daytime sleepiness, or impact cognitive status, but a lack of high-quality sleep may have the same effects, and thus a risk-versus-benefit consideration is necessary. In the author's experience, it is best to avoid the regular use of benzodiazepine hypnotics for sleep given that they are habit-forming, their sudden discontinuation may contribute to seizures, and long-term use can be harmful. However, clonazepam may be helpful in certain situations, such as when patients experience rapid eye movement sleep behavior disorder or other abnormal movements during sleep. Hypnotic agents such as zolpidem or drugs such as trazodone have only been evaluated in small cohorts of patients with some benefit noted, but there also appear to be large population cohort studies that highlight possible adverse impacts of using hypnotic agents in patients with brain cancer.[56,57] Until there is more clear evidence, trials of any drugs should start low and with slow titration, close monitoring, and appropriate evaluation of drug interactions and cardiac status.

KEY POINTS

- Existential distress is also a prevalent symptom in patients with brain tumors and can be very troubling. Despite limited treatment options, this distress should be validated and referral for psychological interventions should be considered.
- Psychiatric symptoms ranging from anhedonia and disinhibition to agitation or mania may present during the CNS tumor disease course and may be managed with sedatives or antipsychotics.
- Poor sleep quality is a common symptom in patients with CNS tumors with a direct impact on overall well-being. Optimization requires addressing potential contributing factors and considering both nonpharmacologic and pharmacologic interventions.

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Fatigue

Fatigue is one of the most common symptoms experienced by patients with brain tumors, with a prevalence ranging from 40% to 70%.[51] Fatigue can be debilitating and severe. The disease, intracranial edema, sleep quality, mood disturbance, decreased physical activity, and medications can all contribute to fatigue, although radiation therapy remains the most common cause.[58,59] Medications (including supplements) and their dosing schedules should be carefully reviewed. Addressing pain and mood, optimizing blood counts (addressing anemia or leukopenia) and nutritional status, and evaluating for hormonal changes or vitamin deficiencies (including thyroid and cortisol levels) is important, especially if the patient has been on long-term steroids. Patients should be counseled to consider energy conservation and prioritize goals and tasks. Naps may be necessary but should be kept short and limited to earlier in the day to not further disturb the sleep-wake cycle. Methylphenidate, modafinil, and armodafinil have been studied in patients with brain tumors who have

CASE 1

A 37-year-old woman was diagnosed with a World Health Organization grade 2 pontomedullary astrocytoma. Soon after biopsy, she was started on radiation therapy and chemotherapy with temozolomide. Within 1 week, she noted significant nausea and dysgeusia from the radiation therapy and oral chemotherapy and subsequently lost 5 pounds. She was given ondansetron, which caused severe constipation. She had a history of anxiety and depression which had been well controlled, but her mood rapidly declined, and she was often tearful and overwhelmed. The fatigue she experienced was "worse than anything else I've experienced."

She started weekly visits to troubleshoot symptoms and met with team members specialized in palliative care. Her antiemetic medication was changed to metoclopramide, with a granisetron patch to be used as needed. Constipation was addressed aggressively with magnesium citrate, sennosides, and soluble fiber. She was advised to include stronger acidic and salty flavors in her diet and add fat and protein when possible. With these changes, she started to tolerate treatment better and her weight stabilized. She started to experience some pharyngitis in the later weeks of radiation therapy, and her fatigue increased. She was encouraged to incorporate a daily walk into her schedule and was started on a low dose of dexamethasone oral liquid to swish and swallow during the last 2 weeks of radiation therapy. This helped her dramatically with the pharyngitis, nausea, appetite, fatigue, and mood, allowing her to complete the 6-week treatment regimen. At this point, the dexamethasone liquid was weaned. The patient was relieved to have completed this phase of her treatment, and over the next few weeks her symptoms gradually improved.

COMMENT

This case illustrates some of the common symptoms that can be experienced early during the treatment of brain tumors. Early identification and management of these symptoms (with relatively simple techniques) can have a positive impact on the overall experience of care.

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persistent fatigue.[60-62] Exercise has been found to provide a statistically and clinically significant reduction in fatigue in patients with cancer and is being evaluated in patients with primary brain tumors.[63] Of course, exercise is not always possible for patients who might have focal limb weakness, seizures, or cognitive issues from their disease, but when possible, it should be encouraged. Acupuncture has been found to be an effective and low-risk fatigue intervention in patients with cancer.[64]

Gastrointestinal Distress

As patients initiate drug regimens or undergo radiation therapy, they may often experience gastrointestinal distress, ranging from nausea and vomiting to constipation or diarrhea. These symptoms are primarily related to drug treatment as most chemotherapies are associated with some degree of nausea, and immunotherapy may lead to gut irritation or colitis that results in diarrhea. Currently, randomized controlled trial data on the most effective agents for nausea in patients with brain tumors do not exist, but a trial assessing the efficacy of rolapitant and ondansetron is ongoing (NCT02991456). Ondansetron, a 5-hydroxytryptamine-3 antagonist, is the most widely used antiemetic in this population. It can be quite effective but may lead to constipation and gastroparesis and may cause headaches (CASE 1). A bowel regimen should be started early, especially if frequent or daily use is expected. Granisetron is available as a transdermal system and may cause less constipation but may not always be covered by insurance. Similarly, neurokinin receptor antagonists such as aprepitant can be effective, but also difficult to obtain through insurance. Olanzapine, an atypical antipsychotic and dopamine antagonist, is the only drug with randomized controlled trial evidence in chemotherapy-induced nausea and vomiting; however, it may be sedating and there is a risk of cardiac dysrhythmia due to QT interval prolongation. An ECG should be obtained before initiation and with any dose modification or addition of other QTc-prolonging agents.[65] Other dopamine antagonists such as prochlorperazine or metoclopramide may be used, but all dopamine antagonists carry a risk of extrapyramidal symptoms. Nonpharmacologic options such as essential oils (peppermint or ginger), acupressure wristbands, and lemon and ginger candy or tea are not well supported in the literature, although these are low risk and worth considering as an adjunct.

The detrimental impact of constipation and gastroparesis on quality of life should not be underestimated; they can contribute to headache, nausea, vomiting, abdominal pain, and hemorrhoids. Identification and management may be easier when bowel habits are routinely questioned during clinic visits, with early or prophylactic initiation of mitigating therapies (eg, high-fiber foods or fiber supplements, polyethylene glycol, senna, lactulose). Diarrhea in a patient on active cancer treatment should always raise suspicion for infection (*Clostridium difficile* if recently hospitalized) and a careful review of the treatment regimen. Various targeted therapy agents (eg, dabrafenib, nilotinib) can cause diarrhea, and depending on the severity the dose may need to be adjusted. In patients on immunotherapy, colitis is a consideration and this diagnosis must be excluded since treatment may require steroids and often a pause in therapy. Antidiarrheal medications may be used if infection or inflammation has been excluded.

KEY POINTS

- Fatigue is a common and often debilitating symptom in patients with CNS tumors with multiple contributing factors that require careful assessment and optimization, including addressing medication side effects, improving sleep, laboratory workup, and increasing activity levels when possible.
- Constipation can occur as a side effect of CNS tumor medications or secondary to diet and can be quite uncomfortable without early, effective management.
- Diarrhea in a patient on immunotherapy should prompt a work-up for colitis prior to initiating antidiarrheal therapy.

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KEY POINTS

- Cognitive dysfunction is a common symptom in patients with brain tumors. Radiation therapy is a significant contributor, although recent findings have helped to reduce radiation neurotoxicity.
- Numerous studies have demonstrated the benefit of inpatient rehabilitation for patients with brain tumors, with good functional outcomes and the ability to return home.

Cognitive Disturbance

Almost 90% of patients with malignant brain tumors already have neurocognitive deficits at diagnosis, although how obvious these are on examination and how they impact functional status will vary.[66] As with other symptoms discussed here, contributing factors may include tumor treatment (especially radiation therapy), antiseizure medications, sleep disturbances, depression, and anxiety. These should be mitigated as best as possible. Whole-brain radiation therapy can contribute to significant neurotoxicity; in recent years, efforts have been made to decrease its use in favor of other radiation therapy techniques that are less toxic and may be equally effective.[67] When whole-brain radiation therapy is necessary, avoiding the hippocampus and using memantine was found to lower the risk of neurocognitive toxicity, a finding that has since altered practice.[68] Proton therapy, hypothesized to have less neurocognitive toxicity compared with traditional photon therapy due to its mechanics, has not yet demonstrated this advantage in adults with high-grade tumors; studies are ongoing in patients with lower-grade tumors.[69] Interventions for cognitive dysfunction are greatly needed as it is a significant contributor to dependence, financial toxicity, and care-partner burden. Cognitive dysfunction also impacts decision making and patient autonomy, although this aspect is not often discussed in the literature.

A patient's cognitive decline translates to increased reliance on the care partner and increased fear of the future. Care partners benefit from education and preparedness; if clinicians anticipate that cognitive issues will worsen, this should be presented (with permission) to the patient and care partner together, along with recommendations for support moving forward. Again, providing reassurance and alleviating any blame or guilt the care partner may feel might be necessary. Simply listening and validating their experience with the care recipient is often therapeutic.

The prevalence and high incidence of cognitive decline highlight the need for early conversations about goals of care in this patient population. This intervention can serve to alleviate care-partner distress in the future since they may be asked down the line to make difficult decisions regarding the patient's care.

Focal Motor Deficits

Hemiparesis or hemiplegia in patients with brain tumors may be transient (secondary to edema or postictal in nature) or more permanent (due to tumor growth, ischemia or hemorrhage in the tumor bed, or after surgery). Supportive care for these patients should focus on timely and appropriate referrals to rehabilitation services, including physical medicine and rehabilitation specialists, physical therapy, occupational therapy, personal trainers, and exercise programs. Numerous studies have demonstrated the benefit of inpatient rehabilitation for patients with brain tumors, with good functional outcomes and the ability to return home.[70,71] Outcomes are improved not just at discharge, but months after the rehabilitation stay, with improved or maintained motor and cognitive function.[72,73] Intensive rehabilitation allows patients to maintain their ability to complete their own activities of daily living for longer, thus reducing the burden on care partners. Outpatient rehabilitation has been less studied in this population, but the benefits of exercise and supervised therapy with serious illness are well known and can be extrapolated to these patients as well.[74]

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Patients with focal motor deficits are at risk of deep venous thrombosis and pulmonary embolism, which requires a high degree of suspicion and awareness. Patients and care partners should be encouraged to immediately reach out should they notice any unilateral limb swelling, pain, erythema, warmth, or any acute shortness of breath, chest pain, or hemoptysis. A 2023 study discusses the development of a tool to predict thromboembolism in patients with glioma, which may be helpful and can be integrated into practice.[75]

Caregiving needs are obviously high when patients have weakness that limits their mobility or ability to provide self-care. Evaluation for and arrangement of appropriate medical equipment (eg, wheelchairs, shower rails, walkers, braces, air mattresses) may be necessary to ensure patient safety at home and to alleviate care-partner burden.

Dysphagia

Dysphagia is usually a late-stage symptom in patients with brain tumors and may be suggestive of progressive disease. The mechanism may be due to brainstem or cranial nerve dysfunction from tumor or edema or somnolence from disease-related encephalopathy. Patients may not recognize the severity of their swallowing difficulties and may be at risk for silent aspiration.[76] By the end of life, 85% of patients with brain tumors will have dysphagia.[77] Studies have demonstrated that patients can achieve functional dysphagia improvement with aggressive rehabilitation, similar to patients who have stroke-related dysphagia[78]; therefore, evaluation by speech and language pathologists and consideration of inpatient or outpatient rehabilitation is important. Speech therapists can educate care partners on how to feed their loved ones, including practical tips on textures to include and avoid, when to thicken liquids, and appropriate positioning. The implications of dysphagia are also discussed in the section on end-of-life care.

Gait Impairment

Gait impairment can be caused by the CNS tumor and its effects (eg, edema, intracranial pressure, hydrocephalus, focal weakness) or by treatment. This symptom can lead to increases in falls and injuries and increased dependence on assistive devices (eg, canes, walkers, wheelchairs). Apart from negatively impacting the patient's morale and self-esteem, this reliance dramatically increases care-partner burden. Physical therapy and rehabilitation may provide functional gains, as discussed above. Home safety assessments work to ensure that the home environment is appropriately set up to meet the patient's needs and reduce the risk of falls. Low-risk interventions like tai chi and qigong have been studied in older adults and people with movement disorders and were found to decrease the incidence of falls.[79,80]

Incontinence

Bowel and bladder incontinence is generally a late symptom in patients with malignant brain tumors (incidence of 40% by end of life).[81] It may be secondary to frontal lobe injury, global encephalopathy and decreased awareness, or seizures, or it may be mechanical in nature due to motor weakness and limited mobility. Incontinence is obviously distressing for the patient; it can be embarrassing and cause a great deal of shame and guilt at the additional burden it places on their loved ones. This symptom can be very taxing for care partners;

KEY POINTS

- **Focal limb weakness in patients with CNS tumors can significantly limit a patient's independence, increase care needs, and increase their risk for venous thrombosis or embolism.**
- **Swallowing difficulties in patients with CNS tumors may come to attention long after onset when they have become severe enough to cause aspiration and complications.**
- **Gait impairment in patients with CNS tumors can be very limiting for the patient and increase their dependence on care partners and should be addressed with early and aggressive physical therapy and appropriate arrangement of assistive devices.**
- **Incontinence is a physically and emotionally challenging symptom for patients with CNS tumors and their care partners; feelings around this topic should be explored and validated, and support should be provided in the form of education and training.**
- **Communicating with seriously ill patients with CNS tumors and their care partners requires a nuanced approach, balancing hope, compassion, and honesty. Information needs and preferences should be elicited and respected and conversations should focus on hoping for the best while also preparing for all possible outcomes.**

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patients may require adult diapers and frequent changing, which is physically challenging and requires frequent nighttime awakenings. Incontinence remains under-researched in terms of interventions that can improve patient and care-partner outcomes, for patients with brain tumors and those with serious illness in general.[82] Care partners often express a lack of preparation and support for this symptom, and education and instruction from nursing staff on efficient diaper changing and skin care management can be beneficial. A bedside plastic urinal, condom catheter, or external banana catheter may be useful, although they may not be covered by insurance.

COMMUNICATION PRINCIPLES

Given the high morbidity and early mortality associated with most neuro-oncologic diagnoses, skilled, compassionate, and patient-centric communication is important. Palliative care delivered by the primary team should include the ability to conduct difficult conversations throughout the disease course, from breaking the news of diagnosis or recurrence to discussing prognosis and goals of care. While formal palliative care may be needed at certain points, the primary clinical team, who has observed the patient's trajectory from the beginning, may be better able to speak to the expected course and generally has an established rapport with the patient and their loved ones.

The initial phase of receiving a diagnosis and seeking out treatment options or opinions can be extremely overwhelming and distressing for patients and loved ones, who are often unable to process the large amounts of information they are receiving.[83] Qualitative studies have illustrated the importance of time, reinforcement of information, and maintenance of hope.[83] It is important to tailor communication style and information to the individual patient and care partner.[84,85] The initial visits provide an opportunity to gauge current understanding and explore information needs and preferences, which might differ between the patient and care partner. As time goes on and clinicians build rapport and gain trust, conversations on difficult subjects such as expected disease course, goals of care, and prognosis may be gently initiated. Patients and their loved ones may bring up this topic themselves, or the situation may necessitate it (eg, disease or progression, treatment change, significant clinical deterioration). Making such conversations a routine, nonthreatening, and nonurgent part of care by integrating them into routine visits may be an important strategy to reduce the fear associated with these topics. Over time, the clinician should make an effort to elicit questions and concerns about the prognosis and expected course and address these honestly but with empathy and compassion. By exploring values, preferences, goals, and acceptable limits to care, clinicians might be able to guide patients and loved ones into realizing what is feasible and what may be unachievable, thus attempting to balance hope with reality.

Several models of communication training now exist for serious illness care, including VitalTalk and the Serious Illness Conversation Guide, which provide useful frameworks for these conversations.[86,87] Communication strategies inspired by these frameworks and examples of appropriate language are listed in TABLE 1.[86,87]

PLANNING FOR THE FUTURE

Conversations on prognosis are important and necessary for the patient and their loved ones, but this is a sensitive area due to the inherent uncertainty involved.

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Communication Strategies and Examples[a]

TABLE 1

Goal	Examples
Create a supportive, open environment	Quiet, private room, with seating for everyone including clinicians
	Dedicated time to building rapport at each visit, asking questions about values, goals, and upcoming milestones
	"In my practice, I like to take some time to routinely check in with my patients about where we are and where we're going."
Assess current understanding; explore reasoning	"What have you been told thus far about this diagnosis?"
	"May I ask: Is there anything you are worried about right now? Has anything prompted your question regarding prognosis?"
Respect boundaries; seek permission	"Would it be okay if I talked a bit more about what we understand of your condition?"
	"Would you like to talk about what patients with this condition can expect?"
Assess needs and information preferences[b]	"How do you like to receive difficult news?"
	"Do you prefer details, or a big picture overview?"
	"Is there someone else you would like us to include in these conversations?"
Give time and space to process	"I want to pause here and take some time to see what questions you have on what we've discussed thus far."
Expect, normalize, and respond to emotional responses	"I can't imagine how hard this must be to hear."
	"I can see how devastating this news is. Our team will be here to support you."
Align with goals and preferences	"I recall you had mentioned that you would want to continue to explore treatment as long as you are able to be independent with daily living; is that still accurate?"
	"I am concerned that you may have more side effects if you choose this treatment option, and I recall you sharing with me that you are hoping for treatment that allows for the best quality of life; I want to be sure we are mindful of that."
Use open-ended, exploratory questions	"What are you hoping for?"
	"Is there anything you are worried about or afraid of?"
	"What do you value most about your life right now?"
	"Can you describe what a good day is for you?"
Share worries and concerns	"I worry that the tumor may be growing in an area where your ability to speak could be affected. Would it be okay if we talked about what that might mean?"
Balance hope with information, especially when sharing difficult news	"I am very hopeful that this new medication will help control your seizures. However, I do want to share my concern that the increase in seizures might suggest tumor growth."
Identify a decision maker or surrogate	"In the rare situation you are unable to speak for yourself, we want to make sure that we turn to the right people who understand your wishes and preferences; who is that person for you?"

[a] Data from VitalTalk[86] and Ariadne Labs.[87]
[b] May differ between patients and care partners.

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Clinicians involved in the patient's care must recognize that prognosis is not simply about life expectancy, but also about the trajectory of a patient's function, capability, clinical condition, and dependence. Studies regarding cancer and other types of serious illness demonstrated that patients who better understood their prognosis were more likely to have care that was in line with their own values and goals and prioritized their comfort and peace.[88] Care partners similarly find prognostic information to be very important, as it can help them feel better prepared and reduce their fear and anxiety for the future.[89] There are also benefits to the clinician and medical system, as patients with a better understanding of their prognosis are less likely to spend time in the hospital at the end of life and have fewer unwanted and high-cost interventions.[90] Concern that these conversations will take away hope or depress patients is not always well founded, and the style of communication and the way information is presented has a great deal to do with how it is received and processed.[91]

When patients and their loved ones are given a diagnosis of a brain tumor, especially one that is malignant, it is common for them to wonder "How much time do I have?" and "What quality of life will I have?" At this early point, it is difficult to provide answers, given the complexities associated with prognostication in this field.[92] Clinicians in this situation may be tempted to quote a number from the literature that is representative of median survival with the disease and may not represent the individual patient's journey; however, this should not be the only message given to the patient.[93,94] Current paradigms for palliative care encourage using time ranges (eg, "months to years" or "weeks to months") instead of providing more specific timelines or numbers, given the uncertainty and inaccuracy inherent in these predictions (which patients and loved ones do hold on to).[95] Questions about prognosis may need to be addressed by helping to develop a roadmap for what lies ahead and by setting expectations for lives disrupted by the diagnosis. Information on what to expect can be empowering, provide a sense of control in an otherwise chaotic and painful situation, and may allow the patient's loved ones to feel informed and able to prepare. Establishing an attitude of "hoping for the best, preparing for the worst" while normalizing the fear and discomfort that come with the diagnosis can be helpful strategies.

Over the disease course, prognostic awareness can become more important and in particular should be explored when considering a significant decision, such as treatment changes or a major intervention like clinical trial enrollment or another surgery. The practice of shared decision making (and informed consent) itself requires that both parties understand the typical outcomes of a diagnosis, with or without the offered intervention. Patients and their loved ones require a sense of what their future holds so they can be prepared to have much-needed conversations, make appropriate arrangements, and plan their legacy. These steps not only provide peace to the patient but also alleviate distress and trauma for care partners who are often required to make surrogate decisions toward the end of life. Small studies have noted that 60% of patients with malignant glioma were not aware of their limited life expectancy.[84] Indeed, a patient's own understanding of their condition can fluctuate dramatically, often leaning toward unrealistic optimism, and be quite discordant from that of their care partners and clinicians.[96] This may be due to a strong sense of hope, cognitive impairment that impacts the ability to process and retain information, or frontal dysfunction affecting insight and judgment.[84] Care partners may better

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understand the incurable nature of the disease and may have different information needs that require separate attention and time.[89,96]

Understanding what lies ahead is important, but this understanding fluctuates and can vary dramatically between patients, care partners, and clinicians, resulting in potential miscommunication and discord.[96] In the author's experience, conversations on prognosis should occur routinely, in a longitudinal fashion, throughout the disease course, with (1) appropriate consideration of a patient's willingness and readiness (as well as that of loved ones); (2) a comfortable setting with dedicated, focused time; (3) the involvement of all necessary stakeholders; and (4) a communication style that is honest and compassionate and that makes room for any emotional response. FIGURE 1 illustrates this four-pronged approach to conversations on prognosis.

Even though the disease may recur or progress, it is possible to hope with the patient while still acknowledging the serious nature of the disease. A strategy highlighted by Jacobsen and colleagues[97] suggests that approaching prognostic conversations from a perspective of maintaining optimistic hopes and helping the patient live well, while still being aware of the possibility of dying, may be helpful by allowing the clinician to align with patients and loved ones and maintain rapport, but still help them cope with a changing reality over time. Successful conversations require that the clinician be informed of the patient's values, goals, and preferences and be able to align with them without bias or self-interest (TABLE 1).

While a written advance care directive, living will, or both are thought to be helpful documents in advance care planning, it is increasingly recognized that these documents simply capture a moment in time and may not be reflective of the patient's most recent wishes, and do not necessarily improve real world end-of-life care.[98] Instead, clinicians benefit from learning about the patient's values, goals, hopes, definitions of acceptable quality of life, and thoughts on limits for medical interventions. This information may help guide decision making when there is an actual change in condition (CASE 2), versus asking patients to make decisions in advance for hypothetical scenarios. Loved ones might still find questions from a formal living will or advance directive helpful as a guide for these conversations; several resources are listed in the Useful Websites section.

Identifying the patient's trusted surrogate decision maker or health care proxy may be the most important part of advance care planning. The routine

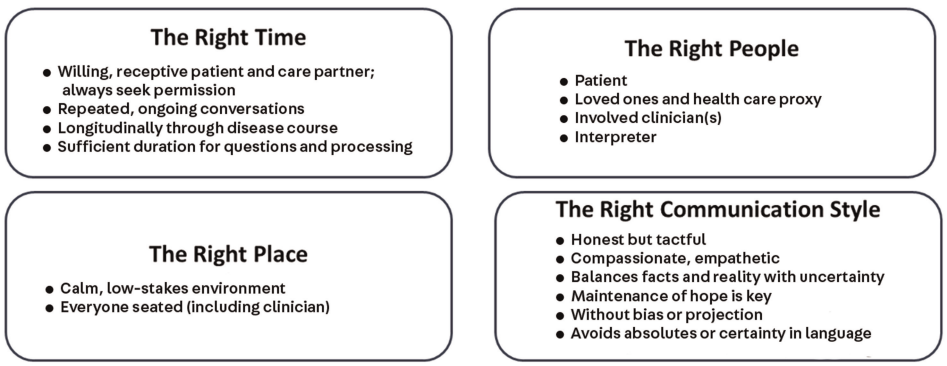

FIGURE 1
A schema for conversations on prognosis.

KEY POINTS

- Planning for the future includes an understanding of one's prognosis, but a level of comfort and trust has to be built prior to having this discussion and all parties involved must understand the significant uncertainty inherent in CNS tumor prognostication.
- Advance care planning for patients with CNS tumors can be helpful when it encourages the patient to think about acceptable quality of life and limits on medical interventions and helps clarify hopes and goals for the future.
- It is best to avoid phrases such as "withdrawal of care" or "stopping all treatment," choosing instead to highlight active interventions like "focusing on managing symptoms" and "ensuring patient comfort."

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incorporation of "Who do you rely on to make health-related decisions for you, if you are unable to?" into visits may prove to be a simple yet effective way of initiating this discussion. If the identified individual is not the legal next of kin, appropriate paperwork should be started with the assistance of social workers. The identified health care proxy should henceforth be included in all conversations involving treatment decisions and goals of care.

CASE 2

A 45-year-old man was diagnosed with a left frontoparietal grade 2 meningioma. Over the next decade, he had multiple surgeries, radiation therapy, and participated in clinical trials. Each intervention seemed to work for a while, but then the tumor would slowly start to grow again. During recent visits, the patient and his wife talked with his neuro-oncologist and neurologist (whom he saw for his epilepsy) about his quality of life. He explained that after the last surgery, he developed right-sided weakness and more seizures. He was no longer able to drive or play golf, and he worried he might need to stop working. He expressed that he was feeling "diminished." He also noted that he was grateful to be alive. His son would be graduating next year, and his daughter was getting married soon, so he would like to be there for those events, but he worried about being unable to do basic tasks like showering or dressing himself. He did not want to have to depend on his wife for everything. "I would absolutely hate that," he stated.

A year later, the patient was rushed to the hospital with status epilepticus. Imaging revealed the tumor had grown yet again, and the pressure was causing significant mass effect, resulting in an acute stroke. With the administration of high-dose steroids and additional antiseizure medications, he was more awake, but had significant expressive aphasia, could not swallow, and his right side was completely paralyzed. The neurosurgeon explained that debulking surgery would not improve his current functional status. Over the next few days, the patient's loved ones tried their best to communicate with him about his wishes moving forward. The patient's wife and doctors recalled the conversations they had earlier and explained that the patient expressed that he did not want to be stuck in his bed and dependent on others. The patient's wife and their children eventually decided to take him home on hospice care. The patient declined rapidly but remained comfortable, and died a week later, surrounded by his family.

COMMENT

This case highlights how eliciting values and goals and discussing acceptable quality of life can help inform goals of care later in the disease process. While these conversations are not easy, familiar providers with good rapport can make patients and loved ones feel more comfortable sharing their hopes and concerns and talking about all possible future outcomes. This is helpful when a crucial decision-making point presents itself.

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END OF LIFE

With most neuro-oncologic diagnoses, the end of life is a gradual process. While death may occur due to a sudden pulmonary embolism or intracranial hemorrhage, these events are rare. More commonly, patients will start to slowly decline, with increased symptom burden in the months to weeks before death (TABLE 2).

When dysphagia develops or worsens during these late stages, artificial feeding is typically avoided as it is unlikely to be a temporary or reversible situation. Artificial nutrition with a nasogastric or percutaneous gastrostomy tube does not change the reality of disease progression and does not lower the risk of complications that generally lead to death in patients with brain tumors (eg, aspiration, infection, embolism, intracranial edema). Instead, it can cause discomfort and may increase both care-partner burden and financial costs. This conversation must be handled with sensitivity and compassion; food intake is closely related to pleasure and strong cultural and religious beliefs can discourage withholding of food and nutrition. This topic should ideally be brought up early in the disease course to get the patient's input if possible.

Transitioning to hospice or preparing for end-of-life care is a difficult decision for many loved ones. It should first be noted that hospice care, like palliative care, is not a universally accepted or available specialty. It is more widely recognized and accepted in the United States, Canada, England, Ireland, Australia, New Zealand, and many parts of Europe. In much of the rest of the world, palliative care and end-of-life care have been strongly encouraged by organizations such as the World Health Organization but may not yet be an integrated part of practice.[99] Cultural and religious differences have a significant impact on how death and dying are viewed; in many parts of the world, open discussion of this topic is strongly taboo and is feared and unacceptable, especially when coming from the clinical team. In these cultures, hospice or similar services may exist under a different name, if at all, or transitions to care may be simply made without explicit discussion. Care at this phase of life may often be provided by the patient's community, frequently at home. It is beyond the scope of this article

Symptoms at End of Life TABLE 2

- Confusion and disorientation
- Hoarse voice
- Inability to stand or walk
- Increased somnolence and fatigue; sleeping 16 to 18 hours a day
- Lack of appetite or desire to eat
- New or worsening aphasia or dysarthria
- New or worsening bowel incontinence, bladder incontinence, or both
- New or worsening dysphagia
- Persistent hallucinations, agitation, or both
- Seizures that are new or more frequent and harder to control
- Severe abulia and anhedonia

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to discuss the nuances of hospice and end-of-life care across the world; the information below focuses on practice in the United States.

When discussing end-of-life care, it is important to reframe this decision as a change from tumor-directed treatment to interventions geared toward maximizing comfort and control of symptoms. Medical care and attention will not stop when tumor-directed care stops; this clarification is very important, as patients and loved ones often fear abandonment. It is best to avoid phrases such as "withdrawal of care" or "stopping all treatment," choosing instead to highlight active interventions like "focusing on managing symptoms" and "ensuring patient comfort." Understanding eligibility for hospice care in the United States and what is covered (and not covered) by insurance or benefits programs is important for all involved clinicians (TABLE 3). While hospice can provide additional support, the hands-on day-to-day care is typically provided by the patient's loved ones or hired aides. This level of care can be extremely taxing both physically and emotionally. It is important that loved ones recognize the need for and are able to seek out help through their social circle or paid aides; rarely, these may be available through insurance policies.

A NOTE ON PHYSICIAN-HASTENED DEATH

Concerns over losing control over their own bodies and being a burden to others may prompt patients with malignant, terminal brain tumors to seek out medical aid in dying or legal physician-hastened death.[100] Medical aid in dying is now legal in 11 United States jurisdictions and 10 other countries including Canada, many European countries, New Zealand, and Australia. Laws vary widely by country and state, but in the United States patients generally need to have a life expectancy of 6 months or less and must have decisional capacity. This can be a complex criterion for patients with brain tumors to meet, given that many will have cognitive impairment, communication difficulties, or both, especially during later stages of the disease, resulting in inequitable access to this option compared to other terminal conditions.[101] It is important to note that in 2018, the AAN updated

TABLE 3

Characteristics of Hospice Care in the United States

- Anticipated life expectancy of 6 months or less
- A service provided at home, at a boarding facility, or, less commonly, at a hospital or inpatient hospice unit (only if there are high symptom needs requiring continuous care)
- Cannot continue active disease-directed treatment[a]
- Does not include 24/7 care or in-home caregiving; an on-call line is available for urgent assistance and advice
- Equipment is provided, such as a hospital bed, air pressure mattress, bedside commode, wheelchair, walker, ostomy supplies, oxygen concentrator, nebulizer, and suction equipment
- Multidisciplinary care team including social workers, nurses, chaplains, bath aides, and, rarely, a physical or occupational therapist, all supervised by a physician or advanced practice provider
- Visits are generally a few times a week, until or unless symptom needs grow

[a] Pediatric hospice and hospice via the Veterans Administration do allow for concurrent care.

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its position statement on legal physician-hastened death, leaving the decision to participate or not participate up to "the conscientious judgment of individual members acting on behalf of their patients."[102] Thus, individual neurologists may decide if they wish to advise, discuss, refer, or prescribe medications to aid in dying, of course in accordance with the law where they are practicing.

Patients with a diagnosis of a malignant or terminal brain tumor may consider the idea of medical aid in dying, especially if they are concerned about loss of bodily control, of being a burden to others, and if they are worried about symptoms such as pain at the end of life.[100] Patients may directly inquire about the options available for legally hastened death if they are aware of options in their state or country, or they might express to their trusted clinician their concern over the protracted course of suffering their condition will lead to and inquire about options to shorten this process or hasten death. Clinicians caring for patients with primary or secondary brain tumors may be faced with this request and should be prepared by exploring the legal limitations and nuances in their area of practice and their personal beliefs and stance on this topic. It is important to know the latter primarily so that the patient can be appropriately directed and referred. Crucially, the clinician should keep in mind that their role is not to judge or convince the patient one way or another, but to provide direction and guidance and address the underlying fear, worry, or distress. The patient's decisional capacity at the time of discussion should be evaluated, along with an assessment of any possible cognitive or psychiatric issues that could be playing a role in this request (an important consideration in this patient population).[103] If the patient has decision-making capacity, has insight into their request, and is not being motivated by depression, anxiety, pain, or panic, appropriate next steps such as a referral to formal palliative care should be undertaken.

KEY POINT

- It is best to avoid phrases such as "withdrawal of care" or "stopping all treatment," choosing instead to highlight active interventions like "focusing on managing symptoms" and "ensuring patient comfort."

HEALTH CARE DISPARITIES

As is the case with health care in general, there are significant racial, ethnic, socioeconomic, and gender-based disparities in access to palliative care, symptom management, and communication.[104] A study of 997 individuals receiving dialysis, for example, found significant differences in existential and supportive care needs in those who identified as Asian American, Native Hawaiian or other Pacific Islander, and Black compared with White individuals.[105] These disparities can result in higher-intensity (and potentially futile) care at the end of life, placing a significant financial burden on loved ones and leading to increased trauma.[106,107] The reasons for these disparities need to be explored further, with potential contributions from a lack of availability of palliative care services, justifiable distrust of the medical system in historically oppressed communities, and clinician bias, fear, or discomfort in utilizing culturally informed communication. Intentional action is needed from clinicians treating seriously ill patients from diverse populations. These actions must include careful reflection on how each individual patient and their loved ones are being supported, with consideration of how their background might affect their needs.[108] Given the serious and often terminal nature of brain cancer diagnoses, those involved in the care of patients with brain tumors must be aware of and strive to be trained in culturally competent care. This competency often involves being aware of one's own biases, being curious and informed of different cultures and backgrounds, and being open, unbiased, and respectful when learning of values and preferences that are widely different from one's own.[109]

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CONCLUSION

CNS tumors are extremely challenging diagnoses for the patient and their loved ones. As treatments improve, we continue to hope that these patients will live longer, fuller lives. However, that life will likely be affected by the heavy symptom burdens from the tumor and its treatment. All clinicians involved in the patient's care should understand common symptoms, make efforts to identify them early, and make efforts to manage them appropriately. High-quality evidence to guide this management is limited. Care partners experience a high degree of emotional and physical distress throughout the journey, and their experiences must also be considered, as they impact the patient's own experience. Patients and care partners benefit from being given information and education, having space to voice their concerns, and having their needs assessed and addressed through support groups and counseling.

Communication is an important aspect of care provision to the patient with a serious illness and their loved ones. While specialty palliative care may be appropriate at times, factors including limited availability, appointment burden, and stigma against palliative care prevent timely referral. Therefore, the patient's primary teams must be skilled in the basics of high-value communication, and be comfortable with difficult discussions on diagnosis, prognosis, goals of care, and planning for the future.

USEFUL WEBSITES

AMERICAN BRAIN TUMOR ASSOCIATION COMMYOUNITY CONNECT PROGRAM
This program pairs newly diagnosed patients and caregivers with a "mentor" who has been through a similar diagnosis and journey.

abta.org/patient-mentor-and-mentee

CAREGIVER BLOG
A blog maintained by the Pacific Neuroscience Institute specifically for care partners of patients living with brain tumors.

pacificneuroscienceinstitute.org/blog/caregivers

THE CONVERSATION PROJECT
Provides resources to guide patients and care partners through talking about their wishes for the end of life.

theconversationproject.org

FAST FACTS
This resource provides concise, practical information on a large library of topics for health professionals who are providing care for the seriously ill. It can be an excellent resource as a quick reference, especially for symptom management.

mypcnow.org/fast-facts

FIVE WISHES
A widely accepted advance care planning document that addresses personal, emotional, and spiritual wishes, and is more detailed than the typical state-specific directives.

fivewishes.org

IMERMAN ANGELS
One-on-one cancer support for patients and caregivers.
imermanangels.org/

MEANING-CENTERED GROUP PSYCHOTHERAPY FOR PATIENTS WITH ADVANCED CANCER
A clinician-led, group intervention of eight weekly sessions aimed at enhancing the quality of life of terminally ill patients.

ebccp.cancercontrol.cancer.gov/programDetails.do?programId=24665479

NATIONAL BRAIN TUMOR SOCIETY'S BRAIN TUMOR SUPPORT CONVERSATIONS
An online support group by the brain tumor community for the brain tumor community.

braintumor.org/support-services/support-groups/brain-tumor-support-conversations

THE NEURO-ONCOLOGY PATIENT SURVIVORSHIP CARE PLAN
An adult neuro-oncology patient-specific care plan for survivorship developed as a fillable PDF that can be used by the patient to record information, document their symptoms and medications, and keep track of their treatment plan.

soc-neuro-onc.org/SNO/Resources/Survivorship_Care_Plan.aspx

ORIENTATION TO CAREGIVING
A handbook for care partners of patients with brain tumors, developed by the University of California, San Francisco Caregivers Project.

ucsfhealth.org/-/media/project/ucsf/ucsf-health/pdf/ucsf_caregiver_handbook.pdf

PREPARE FOR YOUR CARE
Free resources for patients and care partners to help simplify advance care planning and choosing a health care proxy.

prepareforyourcare.org

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ROON
An online resource for people navigating complex health conditions, including glioblastoma.

roon.com

SERIOUS ILLNESS CARE
Created by the palliative care team at Ariadne Labs, this program provides resources to clinicians, patients, caregivers, and health systems to encourage better and earlier conversations around goals and values.

ariadnelabs.org/serious-illness-care

SERIOUS ILLNESS MESSAGING
A website that provides handy guides, tips, and easy-to-borrow language that can be used for training health care professionals and when approaching patients and care partners.

seriousillnessmessaging.org

THE SURVIVORSHIP DIARY
A guide to navigating a diagnosis of brain cancer, written by a patient diagnosed with and living with brain cancer. Available as a digital download.

survivorshipdiary.com

VITALTALK
The website for the VitalTalk organization, which trains clinicians who are seeking to advance their communication skills. The website provides various free guides and resources that can help guide serious conversations.

vitaltalk.org

VTE PREDICTION FOR PATIENTS WITH GLIOMA
A diagnostic tool to predict the probability of venous thromboembolism in patients with glioma.

kbellburdett.shinyapps.io/GliomaPredictVTE

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Postreading Self-Assessment and CME Test

By Adam Kelly, MD, FAAN; Allyson R. Zazulia, MD

NEURO-ONCOLOGY

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ARTICLE 1: 2021 WORLD HEALTH ORGANIZATION CLASSIFICATION OF BRAIN TUMORS

1 Which of the following molecular findings is the strongest predictor of poor prognosis in adult diffuse gliomas?

A 1p/19q-codeletion
B *ATRX* variation
C homozygous deletion of the *CDKN2A* locus
D wildtype *IDH*

2 An 11-year-old girl with a 1-month history of headache and gait unsteadiness is found to have a cerebellar mass, which is surgically resected. Histologically, the tumor demonstrates a biphasic pattern of Rosenthal fibers and looser microcystic areas. Genetic testing reveals duplication of the kinase region of *BRAF*. Which of the following tumor types does this child most likely have?

A gangliоglioma
B medulloblastoma
C meningioma
D pilocytic astrocytoma
E pleomorphic xanthoastrocytoma

3 Which of the following is a central nervous system World Health Organization grade 1 tumor that is most associated with tuberous sclerosis?

A central neurocytoma
B dysembryoplastic neuroepithelial tumor
C gangliocytoma
D myxopapillary ependymoma
E subependymal giant cell astrocytoma

4 A 56-year-old man presents with a 2-month history of persistent headache, vomiting, and ataxia. Brain MRI demonstrates a cystic lesion in the left cerebellar hemisphere that enhances after gadolinium administration. Which of the following tumor types does this patient likely have?

A central nervous system neuroblastoma
B ependymoblastoma
C glioblastoma
D hemangioblastoma
E medulloblastoma

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5 **A 56-year-old man is seen in the clinic after a recent hospitalization for a newly discovered brain mass. The patient presented with hemiparesis but has never had a seizure. Final pathology results from a biopsy are still pending, but glioblastoma is suspected based on radiographic features. According to the Society for Neuro-Oncology and European Association of Neuro-oncology guidelines, which of the following is the recommended approach for the use of antiseizure medication in this patient?**

A a preventive antiseizure medication is not recommended for this patient
B a preventive antiseizure medication should be used until the final pathology results are available
C a preventive antiseizure medication should be used until the patient completes any needed radiation therapy
D a preventive antiseizure medication should be used until the patient undergoes surgical resection
E valproate is the recommended antiseizure medication if one is used

6 **A 49-year-old woman, currently undergoing chemotherapy for a central nervous system World Health Organization grade 3 oligodendroglioma, is seen for a neurologic consultation in the hospital. Upon examination, she has tachycardia, hypertension, and a low-grade fever. She is restless, inattentive, and appears to be responding to visual hallucinations. Motor examination is notable for tremulousness and hyperreflexia. An adverse effect of which of the following chemotherapeutic agents is the most likely cause of this patient's presentation?**

A bevacizumab
B lomustine (CCNU)
C procarbazine
D temozolomide
E vincristine

7 **Which of the following is the current median survival time among patients newly diagnosed with a glioblastoma?**

A less than 6 months
B 6 to 12 months
C 12 to 15 months
D 15 to 18 months
E 18 to 24 months

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8 **A 67-year-old man is seen in the emergency department after presenting with several weeks of progressive headaches and cognitive changes, followed by a generalized seizure. Imaging is notable for a large right frontal mass with associated edema causing mass effect, and a glioblastoma is suspected. Which of the following is the preferred approach to the use of corticosteroid therapy in this patient?**

A corticosteroids should be avoided because of the presence of seizure
B dexamethasone should be used at the lowest dose needed to control symptoms
C high-dose dexamethasone should be started and continued indefinitely
D low-dose prednisone should be started and continued through surgical resection
E prophylactic antibiotics should be started if corticosteroids are used

ARTICLE 3: PEDIATRIC NEURO-ONCOLOGY

9 **Exposure to which of the following is the best-established environmental risk factor for pediatric brain tumors?**

A artificial sweeteners
B cellular telephones
C childhood vaccinations
D ionizing radiation
E magnetic fields

10 **Thirty-six hours after an uncomplicated surgical resection of a posterior fossa mass confirmed pathologically as a medulloblastoma, a 5-year-old boy has the onset of mutism, emotional lability, and apraxia. Which of the following outcomes is most likely?**

A development of global aphasia and right hemiparesis
B improvement in speech but persistent neurocognitive deficits
C rapid progression to coma
D spontaneous full recovery within 2 to 5 days
E waxing and waning course with episodic neurologic impairment

11 **Which of the following medications has been approved by the US Food and Drug Administration (FDA) to reduce the risk of ototoxicity from cisplatin in children with localized, nonmetastatic solid tumors?**

A acetazolamide
B dexrazoxane
C hydroxocobalamin
D mesna
E sodium thiosulfate

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12 **A genetic variation in which of the following pathways is present in nearly all patients with pediatric low-grade gliomas?**

A hepatocyte growth factor/mesenchymal epithelial transition factor
B isocitrate dehydrogenase
C mammalian target of rapamycin
D programmed cell death 1/programmed death-ligand 1
E RAS-mitogen-activated protein kinase

ARTICLE 4: CENTRAL NERVOUS SYSTEM LYMPHOMA

13 **A 57-year-old man is undergoing evaluation for a brain mass that was found after presenting with several weeks of worsening headaches. Which of the following imaging features would support a diagnosis of primary central nervous system lymphoma as opposed to glioma or metastatic disease?**

A a coexistent pachymeningeal enhancement
B a heterogenous enhancement pattern
C a high degree of edema relative to lesion size
D an infratentorial location
E the presence of restricted diffusion

14 **Which of the following subsets of patients with primary central nervous system lymphoma should have extensive surgical debulking as part of their treatment approach?**

A all patients
B extensive debulking should not be pursued in most patients
C patients who show partial improvement following steroid treatment
D patients with lesions greater than 2 cm in size
E patients with posterior fossa involvement

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15 **A 67-year-old woman with a history of treatment for primary central nervous system lymphoma is seen in the clinic. She finished treatment 2 years ago and has had no symptoms of recurrence since then. Which of the following would most closely follow the monitoring and surveillance recommendations of the National Comprehensive Cancer Network in this patient?**

A a brain MRI every 3 months for the first 2 years, followed by every 6 months for 3 years, and then annually
B a CT of the head and chest, abdomen, and pelvis annually
C an annual lumbar puncture
D an MRI of the head and entire spinal column every 3 to 6 months
E annual positron emission tomography (PET) for 3 years

16 **Among patients with a diagnosis of systemic lymphoma, what is the probability of central nervous system involvement in any capacity?**

A 1%
B 5%
C 10%
D 18%
E 25%

ARTICLE 5: BRAIN METASTASES AND LEPTOMENINGEAL DISEASE

17 **Malignancies from which of the following organs have the greatest propensity to metastasize to the central nervous system?**

A breast
B colon
C pancreas
D prostate
E stomach

18 **Screening for central nervous system metastasis at the time of cancer diagnosis is recommended for which of the following primary malignancies?**

A angiosarcoma
B *HER2*-negative breast cancer
C plasmacytoma
D renal cell carcinoma
E squamous cell carcinoma

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19 **Four years after treatment for triple-negative breast cancer without recurrence, a 38-year-old woman is admitted to the hospital with a 2-week history of progressive headache and gait unsteadiness. Brain MRI shows a large ring-enhancing right cerebellar mass with surrounding edema resulting in effacement of the fourth ventricle. In addition to corticosteroid administration, which of the following is the most appropriate next step in management for this patient?**

A focal stereotactic radiosurgery
B immune checkpoint inhibitor therapy
C platinum-based chemotherapy
D surgical resection
E whole-brain radiation therapy

20 **Which of the following clinical manifestations in a patient with a primary malignancy is most suggestive of leptomeningeal metastases?**

A aphasia
B cranial neuropathies
C fever
D focal motor seizures
E hemiparesis

ARTICLE 6: SKULL BASE TUMORS

21 **Which of the following is the only well-established environmental risk factor for the development of meningioma, which is estimated to lead to a 6-fold to 10-fold increase in risk of incidence?**

A asbestos exposure
B history of central nervous system infection
C history of ionizing radiation exposure
D history of oral contraceptive use
E vitamin D deficiency

22 **A 74-year-old man is seen in consultation for abnormal brain imaging. He underwent a contrast-enhanced brain MRI as part of a workup for syncope, which revealed an incidental lesion in the region of the right cerebellopontine angle. Which of the following favors a diagnosis of schwannoma as opposed to meningioma in this patient?**

A absence of calcifications
B homogenous contrast enhancement pattern
C hyperostosis of nearby bony structures
D presence of a dural tail of enhancement
E presence of concomitant diffusion restriction

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23 **A 39-year-old woman is seen in the clinic for abnormal imaging findings. She recently underwent brain MRI for headaches, which have subsequently been attributed to migraine and are well-controlled on venlafaxine and minimization of caffeine intake. This study revealed an 8-mm area of contrast enhancement in the pituitary gland; subsequent endocrine workup revealed no abnormalities. Examination is normal, as is a formal visual field assessment. Which of the following is the best next step in management?**

A dopamine agonist therapy
B inferior petrosal sinus sampling
C observation with serial imaging
D stereotactic radiosurgery
E transsphenoidal resection

24 **A 60-year-old woman with a remote history of breast cancer is seen in the clinic for several months of dysphagia and hypophonia. Examination reveals speech changes as well as weakness of the left trapezius. MRI shows a mass in the region of the left jugular foramen with areas of contrast enhancement and flow voids. Which of the following is the most likely diagnosis?**

A chordoma
B ecchordosis physaliphora
C high-grade meningioma
D paraganglioma
E skull-based metastasis from breast cancer recurrence

ARTICLE 7: PARANEOPLASTIC NEUROLOGIC SYNDROMES

25 **Which of the following antibodies is most commonly associated with dream enactment behaviors?**

A α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor
B antineuronal nuclear antibody type 1 (Hu)
C glutamic acid decarboxylase 65 (GAD65)
D leucine-rich glioma inactivated protein 1
E Purkinje cell cytoplasmic antibody type 1 (Yo)

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26 **A 43-year-old man with refractory seizures and hypersomnia is found to have anti-Ma2 antibodies. CT of the chest, abdomen, and pelvis with and without contrast is unrevealing. Targeting of which of the following organs for further screening is most likely to reveal a malignancy in this patient?**

A brain
B colon
C lung
D testicle
E thymus

27 **Which of the following antibody syndromes is most likely to develop within months of herpes simplex encephalitis?**

A contactin-associated proteinlike 2
B glial fibrillary acidic protein (GFAP)
C Ma
D *N*-methyl-D-aspartate (NMDA) receptor
E voltage-gated potassium channel

28 **Screening for which of the following conditions is recommended in patients with stiff person syndrome?**

A cardiomyopathy
B diabetes
C hepatitis
D hyperthyroidism
E nephropathy

ARTICLE 8: NEUROLOGIC COMPLICATIONS OF CONVENTIONAL CHEMOTHERAPY AND RADIATION THERAPY

29 **Which of the following is the most common acute central nervous system toxicity associated with cancer-directed chemotherapy?**

A acute encephalopathy
B aseptic meningitis
C cerebellar syndrome
D nonconvulsive status epilepticus
E transverse myelitis

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30 **A 55-year-old woman currently undergoing chemotherapy for acute leukemia is seen in consultation in the hospital. Her last treatment was 4 days ago. She initially showed some symptoms of encephalopathy, followed by marked bilateral ataxia and slurred speech. High-dose treatment with which of the following chemotherapies is the most likely cause of this patient's presentation?**

A 5-fluoruracil
B cytarabine
C doxorubicin
D methotrexate
E vincristine

31 **Which of the following is the most common clinical presentation of chemotherapy-induced peripheral neuropathy?**

A autonomic neuropathy
B demyelinating sensorimotor neuropathy
C multifocal motor neuropathy
D painful sensory axonal neuropathy
E small fiber neuropathy

32 **A 57-year-old man with a prior history of lung cancer, including treatment with radiation therapy, is seen for symptoms involving his left arm. Which of the following features would be more suggestive of radiation plexopathy, as opposed to neoplastic plexopathy, as the cause of his symptoms?**

A more intense paresthesias
B onset of symptoms within 3 months of treatment
C the presence of myokymic discharges on EMG
D profound weakness
E severe left arm pain

ARTICLE 9: NEUROLOGIC COMPLICATIONS OF CANCER IMMUNOTHERAPY

33 **Which of the following is the most common neurologic syndrome associated with immune checkpoint inhibitor use?**

A central nervous system demyelinating disease
B encephalitis
C meningitis
D myelitis
E myositis

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34 **Which of the following is a typical manifestation of cytokine release syndrome?**

A bradycardia
B constipation
C fever
D hypertension
E rhinorrhea

35 **A 65-year-old woman with melanoma is seen in the clinic with myalgias, fatigue, and difficulty swallowing for the past month. She started ipilimumab 6 weeks prior to symptom onset. Examination demonstrates bilateral ptosis, bifacial weakness, and weakness of the deltoid and iliopsoas muscles bilaterally. Creatine kinase is 1810 U/L. Electrodiagnostic studies demonstrated fibrillation potentials and small motor unit potentials on needle EMG. Ipilimumab is discontinued, and the patient is started on steroids. An evaluation for which of the following additional conditions is most appropriate in this patient?**

A adrenal insufficiency
B hyperparathyroidism
C leptomeningeal metastasis
D myocarditis
E thymoma

36 **Which of the following management strategies is most appropriate for patients with cytokine release syndrome?**

A antithymocyte globulin
B hyperosmolar therapy
C interleukin-6-directed therapy
D intravenous immunoglobulin
E plasma exchange

ARTICLE 10: MANAGEMENT OF COMPLICATIONS IN NEURO-ONCOLOGY PATIENTS

37 **Which of the following is a major advantage of dexamethasone, relative to other glucocorticoid medications, for the treatment of vasogenic cerebral edema from brain tumors?**

A availability in transdermal formulation
B high affinity for protein binding
C little to no mineralocorticoid effect
D low to moderate potency
E short biological half-life

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38 **Corticosteroids such as dexamethasone are known to directly counter the biological effect of which of the following forms of cancer-directed therapy?**

A bevacizumab
B immune checkpoint inhibitors
C methotrexate
D platinum-based chemotherapies
E stereotactic radiosurgery

39 **Which of the following is the best estimate of the prevalence of long-term hypopituitarism (of any degree) following radiation therapy for nasopharyngeal cancer or intracranial tumors?**

A 20%
B 38%
C 51%
D 66%
E 82%

40 **A 71-year-old man with a recent diagnosis of glioblastoma presents to the emergency department with shortness of breath. CT angiogram of the chest reveals pulmonary embolism. CT of the head shows stable tumor size and vasogenic edema, without evidence of hemorrhage. Which of the following is the best next step in management?**

A catheter-based pulmonary artery embolectomy
B enoxaparin
C place inferior vena cava filter, avoid anticoagulation
D rivaroxaban
E warfarin, with a goal international normalized ratio (INR) of 2 to 3

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Postreading Self-Assessment and CME Test—Preferred Responses

By Adam Kelly, MD, FAAN; Allyson R. Zazulia, MD

NEURO-ONCOLOGY

Following are the preferred responses to the questions in the Postreading Self-Assessment and CME Test in this *Continuum* issue. The preferred response is followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the article topic. The comments and references included with each question are intended to encourage independent study.

US PARTICIPANTS: Upon completion of the Postreading Self-Assessment and CME Test and issue evaluation online at continpub.com/CME, participants may earn up to 20 *AMA PRA Category 1 Credits*™ toward SA-CME. US participants have up to 3 years from the date of publication online to earn SA-CME credits.

CANADIAN PARTICIPANTS: This program is an Accredited Self-Assessment Program (Section 3) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the University of Calgary Office of Continuing Medical Education and Professional Development. Refer to the CME tab on ContinuumJournal.com for dates of accreditation. Canadian participants should visit MAINPORT (mainport.org) to record learning and outcomes. Canadian participants can claim a maximum of 20 hours per issue (credits are automatically calculated).

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ARTICLE 1: 2021 WORLD HEALTH ORGANIZATION CLASSIFICATION OF BRAIN TUMORS

1 The preferred response is **D (wildtype *IDH*)**. Glioblastoma, the most malignant form of primary glioma in adults, is characterized by wildtype *IDH*. For more information, refer to **page 1643** of the *Continuum* article "2021 World Health Organization Classification of Brain Tumors."

2 The preferred response is **D (pilocytic astrocytoma)**. The described histopathology of a biphasic pattern of Rosenthal fibers and looser microcystic areas in a pediatric cerebellar tumor with duplication of the kinase region of *BRAF* is most suggestive of pilocytic astrocytoma. For more information, refer to **page 1648** of the *Continuum* article "2021 World Health Organization Classification of Brain Tumors."

3 The preferred response is **E (subependymal giant cell astrocytoma)**. Subependymal giant cell astrocytoma is a central nervous system World Health Organization grade 1 tumor typically arising in the wall of the lateral ventricles that is strongly associated with tuberous sclerosis. For more information, refer to **page 1649** of the *Continuum* article "2021 World Health Organization Classification of Brain Tumors."

4 The preferred response is **D (hemangioblastoma)**. Hemangioblastoma is a benign vascular tumor seen in adults that is characteristically located in the cerebellum and typically appears on imaging as a cystic lesion with contrast enhancement. Central nervous system (CNS) neuroblastoma, ependymoblastoma, and medulloblastoma are pediatric CNS tumors, while glioblastoma most commonly involves the cerebral hemisphere and would not be cystic. For more information, refer to **page 1656** of the *Continuum* article "2021 World Health Organization Classification of Brain Tumors."

ARTICLE 2: ADULT-TYPE DIFFUSE GLIOMAS

5 The preferred response is **A (a preventive antiseizure medication is not recommended for this patient)**. Recent clinical practice guidelines from the Society for Neuro-Oncology and the European Association of Neuro-Oncology recommend against the routine use of antiseizure medications in patients with newly diagnosed brain tumors who have not experienced events concerning for seizures. This recommendation extends across different tumor subtypes and through different phases of treatment (eg, surgery). For more information, refer to **page 1664** of the *Continuum* article "Adult-type Diffuse Gliomas."

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6 The preferred response is **C (procarbazine).** This patient's clinical presentation is highly suggestive of serotonin syndrome. Her central nervous system World Health Organization grade 3 oligodendroglioma is likely being treated with a chemotherapy regimen consisting of procarbazine, lomustine (CCNU), and vincristine. Of these agents, procarbazine has the potential for some monoamine oxidase inhibitor (MAOI) activity, and as such could precipitate serotonin syndrome in the setting of certain concomitant medications, dietary choices, or both. For more information, refer to **page 1672** of the *Continuum* article "Adult-type Diffuse Gliomas."

7 The preferred response is **D (15 to 18 months).** Despite treatment advances including surgery, radiation therapy, temozolomide and tumor-treating fields, survival time estimates among patients with glioblastomas remain somewhat pessimistic. At present, the median overall survival time in glioblastoma is estimated at 15 to 18 months. For more information, refer to **page 1663** of the *Continuum* article "Adult-type Diffuse Gliomas."

8 The preferred response is **B (dexamethasone should be used at the lowest dose needed to control symptoms).** Any brain neoplasm, but especially high-grade gliomas, can be associated with vasogenic cerebral edema that can contribute to a patient's symptoms. Corticosteroid therapy can be considered to help with symptom control, though due to concerns for long-term toxicity corticosteroid treatment (usually dexamethasone) should be used at the lowest dose and for the shortest duration of time needed for symptom relief. For more information, refer to **page 1664** of the *Continuum* article "Adult-type Diffuse Gliomas."

ARTICLE 3: PEDIATRIC NEURO-ONCOLOGY

9 The preferred response is **D (ionizing radiation).** The best-established environmental risk factor for pediatric brain tumors is exposure to ionizing radiation, such as that from therapeutic radiation therapy. There is no consistent support for causal associations with any of the other exposures. For more information, refer to **page 1681** of the *Continuum* article "Pediatric Neuro-oncology."

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10 The preferred response is **B (improvement in speech but persistent neurocognitive deficits).** The onset of mutism, emotional lability, and apraxia within days of surgical resection of a posterior fossa tumor is the hallmark of postoperative cerebellar mutism syndrome, which affects more than one-quarter of children with medulloblastoma. Language recovery occurs within 6 months in virtually all cases, but long-term neurocognitive deficits are the norm. The pathophysiology is incompletely understood, but disruption of the cerebellar outflow tracts is thought to play a role. For more information, refer to **page 1694** of the *Continuum* article "Pediatric Neuro-oncology."

11 The preferred response is **E (sodium thiosulfate).** Platinum-based chemotherapeutic agents can cause irreversible ototoxicity. Studies investigating otoprotective agents in patients who are taking these agents are ongoing, and in 2022, the US Food and Drug Administration (FDA) approved sodium thiosulfate to reduce the risk of ototoxicity associated with cisplatin in patients 1 month old and older with localized, nonmetastatic solid tumors. For more information, refer to **page 1701** of the *Continuum* article "Pediatric Neuro-oncology."

12 The preferred response is **E (RAS–mitogen-activated protein kinase [RAS-MAPK]).** The vast majority of pediatric low-grade gliomas are driven by a single genetic event resulting in up-regulation of the RAS-MAPK pathway. While *IDH* variations occur in approximately three-quarters of adult low-grade gliomas, they are quite rare in pediatric low-grade gliomas. For more information, refer to **page 1682** of the *Continuum* article "Pediatric Neuro-oncology."

ARTICLE 4: CENTRAL NERVOUS SYSTEM LYMPHOMA

13 The preferred response is **E (the presence of restricted diffusion).** Solitary brain lesions can be seen in the setting of primary central nervous system (CNS) lymphoma, gliomas, or CNS metastatic disease. Imaging features vary somewhat between these possibilities and may help guide early management and diagnostic testing. In this case, the presence of diffusion restriction may distinguish the lesion as being related to lymphoma as opposed to other possibilities. For more information, refer to **page 1712** of the *Continuum* article "Central Nervous System Lymphoma."

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14 The preferred response is **B (extensive debulking should not be pursued in most patients)**. Although some patients can have lesions that are relatively large in size, extensive surgical debulking is typically not recommended as a treatment approach in patients with primary central nervous system lymphoma. This is for a number of reasons, including the infiltrative nature of the disease and its typical responsiveness to steroid therapy. For more information, refer to **page 1712** of the *Continuum* article "Central Nervous System Lymphoma."

15 The preferred response is **A (a brain MRI every 3 months for the first 2 years, followed by every 6 months for 3 years, and then annually)**. The National Comprehensive Cancer Network has established monitoring guidelines to evaluate for the presence of relapse in patients who have had treatment for primary central nervous system lymphoma. These include recommendations for brain MRI every 3 months for the first 2 years, followed by every 6 months for 3 years, and then annually. For more information, refer to **page 1717** of the *Continuum* article "Central Nervous System Lymphoma."

16 The preferred response is **B (5%)**. The majority of patients with a diagnosis of systemic lymphoma will not have extension of their disease to the central nervous system (CNS) space; this probability is generally estimated at 5%. This risk can be higher in certain patient populations; therefore, investigation for CNS involvement may be warranted. For more information, refer to **page 1718** of the *Continuum* article "Central Nervous System Lymphoma."

ARTICLE 5: BRAIN METASTASES AND LEPTOMENINGEAL DISEASE

17 The preferred response is **A (breast)**. Breast cancer, lung cancer, and melanoma are the malignancies with the greatest propensity to metastasize to the central nervous system, although any primary tumor can do so. For more information, refer to **page 1727** of the *Continuum* article "Brain Metastases and Leptomeningeal Disease."

18 The preferred response **is A (angiosarcoma)**. According to the National Comprehensive Cancer Center guidelines, screening for central nervous system metastasis at the time of diagnosis is only recommended for patients with select malignancies, including small cell lung cancer, non-small cell lung cancer, melanoma, testicular cancer, alveolar soft part sarcoma, angiosarcoma, and left-sided cardiac sarcoma. For more information, refer to **page 1729** of the *Continuum* article "Brain Metastases and Leptomeningeal Disease."

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19 The preferred response is **D (surgical resection).** While stereotactic radiosurgery has become the mainstay for the treatment of brain metastases, surgery may be the preferred treatment strategy in certain settings such as large brain metastases associated with increased intracranial pressure or neurologic deficits and in patients like this one with posterior fossa metastases at risk for obstructive hydrocephalus. For more information, refer to **page 1731** of the *Continuum* article "Brain Metastases and Leptomeningeal Disease."

20 The preferred response is **B (cranial neuropathies).** The clinical manifestations of leptomeningeal metastases reflect dysfunction of the cranial and spinal nerves that course through the subarachnoid space. They may also include headache associated with meningeal irritation, increased intracranial pressure and encephalopathy related to metabolic depression of the cerebral hemispheres, or both. For more information, refer to **page 1738** of the *Continuum* article "Brain Metastases and Leptomeningeal Disease."

ARTICLE 6: SKULL BASE TUMORS

21 The preferred response is **C (history of ionizing radiation exposure).** Meningiomas are common, representing the most common type of intracranial brain tumor. Despite this high frequency, epidemiologic studies have only identified a history of ionizing radiation exposure as an environmental risk factor for the development of meningioma. For more information, refer to **page 1753** of the *Continuum* article "Skull Base Tumors."

22 The preferred response is **A** (**absence of calcifications**). Contrast-enhancing lesions in the cerebellopontine angle region are relatively common findings and are usually related to vestibular schwannoma or skull-based meningioma (or less likely epidermoid cyst). Although some imaging overlap occurs between these possibilities, some features can help distinguish schwannoma from meningioma. Specifically, the enhancement pattern of schwannoma can be less homogenous than that of meningioma, and calcifications, which are common with meningioma, are generally not seen in schwannoma. For more information, refer to **page 1757** of the *Continuum* article "Skull Base Tumors."

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23 The preferred response is **C** (**observation with serial imaging**). This patient is presenting with an incidental pituitary lesion, which appears to be a nonfunctioning pituitary adenoma. Given the small size of this finding, the lack of any endocrine abnormalities, and the absence of any compression on the optic nerves or other nearby structures, observation is an appropriate strategy in this patient. For more information, refer to **page 1764** of the *Continuum* article "Skull Base Tumors."

24 The preferred response is **D** (**paraganglioma**). This patient is presenting with symptoms of cranial nerve dysfunction, specifically affecting cranial nerves IX, X, and XI, and imaging showing a mass lesion in the region of the left jugular foramen. This presentation would be consistent with a jugular foramen paraganglioma (glomus tumor), which is further supported by the imaging features of contrast enhancement and flow voids (salt and pepper appearance). For more information, refer to **page 1773** of the *Continuum* article "Skull Base Tumors."

ARTICLE 7: PARANEOPLASTIC NEUROLOGIC SYNDROMES

25 The preferred response is **D (leucine-rich glioma inactivated protein 1 [LGI1])**. Sleep disturbances, such as insomnia, hypersomnia, parasomnias, and snoring, are common in autoimmune encephalitis. Dream enactment behaviors are particularly common in patients with anti-LGI1 antibodies, occurring in up to one-half of patients at the time of symptom onset. For more information, refer to **page 1780** of the *Continuum* article "Paraneoplastic Neurologic Syndromes."

26 The preferred response **is D (testicle).** Anti-Ma2 antibody–associated paraneoplastic syndromes frequently present with symptoms of limbic, diencephalic, or brainstem dysfunction and most commonly occur in men with testicular germ cell tumors. Thus, in the setting of unrevealing CT this patient should undergo testicular ultrasound and serum α-fetoprotein. For more information, refer to **page 1788** of the *Continuum* article "Paraneoplastic Neurologic Syndromes."

27 The preferred response is **D (*N*-methyl-D-aspartate [NMDA] receptor).** Herpes simplex virus (HSV) encephalitis may be a trigger for the development of anti-NMDA receptor antibodies, with NMDA receptor encephalitis occurring within 4 months in approximately one-quarter of patients with HSV encephalitis. For more information, refer to **page 1787** of the *Continuum* article "Paraneoplastic Neurologic Syndromes."

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28 The preferred response is **B (diabetes).** Anti-glutamic acid decarboxylase (anti-GAD) antibodies are linked with both autoimmune diabetes and stiff person syndrome; thus, screening for diabetes is recommended, especially in patients who will be receiving corticosteroids and glucose-containing intravenous immunoglobulin (IVIg). For more information, refer to **page 1796** of the *Continuum* article "Paraneoplastic Neurologic Syndromes."

ARTICLE 8: NEUROLOGIC COMPLICATIONS OF CONVENTIONAL CHEMOTHERAPY AND RADIATION THERAPY

29 The preferred response is **A (acute encephalopathy).** Cancer-directed chemotherapies are associated with a number of acute syndromes affecting the central and peripheral nervous systems. Of these, acute encephalopathy is the most common and has been associated with a variety of different chemotherapy regimens. For more information, refer to **page 1810** of the *Continuum* article "Neurologic Complications of Conventional Chemotherapy and Radiation Therapy."

30 The preferred response is **B (cytarabine).** This patient is presenting with an acute cerebellar syndrome several days following treatment with chemotherapy. Of the options listed, high-dose cytarabine is the most likely agent to cause this presentation, including symptoms of encephalopathy that precede the cerebellar findings. For more information, refer to **page 1810** of the *Continuum* article "Neurologic Complications of Conventional Chemotherapy and Radiation Therapy."

31 The preferred response is **D (painful sensory axonal neuropathy).** Different chemotherapeutic agents can be associated with different manifestations of chemotherapy-induced peripheral neuropathy. That being said, the most common presentation is a distal painful sensory axonal neuropathy, following a stocking-and-glove distribution. For more information, refer to **page 1812** of the *Continuum* article "Neurologic Complications of Conventional Chemotherapy and Radiation Therapy."

32 The preferred response is **C (the presence of myokymic discharges on EMG).** Weakness and sensory changes in an upper extremity in a patient with cancer can be caused by a number of possibilities, including neoplastic infiltration and radiation plexopathy. Certain clinical and electrophysiologic features can be helpful in distinguishing between these two diagnoses; of the options listed, the presence of myokymic discharges on EMG would be most strongly correlated with a radiation plexopathy. For more information, refer to **page 1823** of the *Continuum* article "Neurologic Complications of Conventional Chemotherapy and Radiation Therapy."

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ARTICLE 9: NEUROLOGIC COMPLICATIONS OF CANCER IMMUNOTHERAPY

33 The preferred response is **E (myositis).** Neuromuscular disorders account for more than one-half of neurologic adverse events associated with immune checkpoint inhibitor use, with myositis accounting for approximately 32% and neuropathies for approximately 22%. For more information, refer to **page 1828** of the *Continuum* article "Neurologic Complications of Cancer Immunotherapy."

34 The preferred response is **C (fever).** Cytokine release syndrome is a systemic inflammatory response that can be associated with chimeric antigen receptor T-cell therapy. The syndrome is characterized by fever, hypotension, and hypoxia, which may progress to multiorgan failure. For more information, refer to **page 1836** of the *Continuum* article "Neurologic Complications of Cancer Immunotherapy."

35 The preferred response is **D (myocarditis).** This patient's clinical presentation of oculobulbar and proximal muscle weakness with elevated creatine kinase and muscle fiber irritability on EMG is consistent with immune checkpoint inhibitor (ICI)-induced myositis. Since as many as 30% of patients with ICI-induced myositis may also have myocarditis, evaluation for myocarditis is most appropriate in this patient. For more information, refer to **page 1830** of the *Continuum* article "Neurologic Complications of Cancer Immunotherapy."

36 The preferred response **is C (interluekin-6 [IL-6]–directed therapy).** IL-6-directed therapy, including the IL-6 antagonist siltuximab and the IL-6 receptor antagonist tocilizumab, is most appropriate for the management of cytokine release syndrome. For more information, refer to **page 1836** of the *Continuum* article "Neurologic Complications of Cancer Immunotherapy."

ARTICLE 10: MANAGEMENT OF COMPLICATIONS IN NEURO-ONCOLOGY PATIENTS

37 The preferred response is **C (little to no mineralocorticoid effect).** Glucocorticoid therapy is a mainstay of treatment in neuro-oncology, as these medications are highly effective for the management of cerebral edema. Of the available options, dexamethasone is preferred for a number of reasons, including its lack of any significant mineralocorticoid effect. For more information, refer to **page 1849** of the *Continuum* article "Medical Care of Neuro-oncology Patients."

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38 The preferred response is **B (immune checkpoint inhibitors [ICIs])**. ICIs, as their name suggests, harness the function of the immune system to attack certain types of malignancies, with considerable effects on overall survival. Corticosteroids have an immunosuppressive effect and would be expected to counteract the effect of ICIs. For more information, refer to **page 1857** of the *Continuum* article "Medical Care of Neuro-oncology Patients."

39 The preferred response is **D (66%)**. Hypopituitarism, in varying degrees, is a known long-term complication of radiation therapy for head and neck cancers, including brain tumors. Despite its known occurrence, the prevalence of hypopituitarism is higher than most expect, suggesting that this syndrome may be underrecognized and undertreated by providers. For more information, refer to **page 1859** of the *Continuum* article "Medical Care of Neuro-oncology Patients."

40 The preferred response is **D (rivaroxaban)**. Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is common among patients with primary brain tumors and central nervous system metastases. While anticoagulation does pose a risk of hemorrhage into a brain lesion, the overall benefits of anticoagulation are felt to outweigh the risks in VTE. Among the various options, current evidence supports the use of direct oral anticoagulants (like rivaroxaban) over low-molecular-weight heparin or warfarin. For more information, refer to **page 1863** of the *Continuum* article "Medical Care of Neuro-oncology Patients."

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ERRATUM

In the October 2023 issue of *Continuum* (Peripheral Nerve and Motor Neuron Disorders, Vol. 29, No. 5), the following error occurred:

In the article "Guillain-Barré Syndrome" by Ali A. Habib, MD, and Waqar Waheed, MD (*Continuum: Lifelong Learning in Neurology* 2023:29:1340 and 1343), the unit of measure for the cell count for CSF pleocytosis was incorrectly shown as "50 × 10/L." The correct unit of measure is shown below. The last bullet point on page 1340 should read "CSF pleocytosis (greater than 50 × 10^6/L), particularly if polymorphonuclear cells are prominent". Table 2-3 on page 1343 should read "**CSF pleocytosis (>50 × 10^6/L)**".

Habib AA, Waheed W. Guillain-Barré syndrome. Continuum (Minneap Minn) 2023;29(5, Peripheral Nerve and Motor Neuron Disorders): 1327-1356. doi:10.1212/CON.0000000000001289

DIFFERENTIAL DIAGNOSIS

Diagnosis is relatively straightforward when a patient exhibits typical GBS symptoms, but the diagnosis can be challenging in patients with atypical presentations. Red flags suggesting a diagnosis other than GBS include the following[2,50]:

- Severe respiratory dysfunction with limited limb weakness at onset
- Slow progression over 4 weeks without cranial nerve, autonomic, or respiratory involvement
- Severe sensory signs with limited weakness at onset
- Bladder or bowel dysfunction at onset
- Sharp sensory level on torso
- Marked persistent asymmetric weakness
- Fever at onset
- CSF pleocytosis (greater than 50 × 10^6/L), particularly if polymorphonuclear cells are prominent

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Presentation	Differential diagnosis
Severe diaphragmatic weakness with limited limb weakness at the onset When the severity of respiratory muscle weakness is disproportionate to limb weakness, the differential diagnosis should expand accordingly	Myasthenia gravis, high cervical cord intramedullary lesions (eg, tumor, abscess, inflammatory disease), Pompe disease, botulism, hypermagnesemia, or hypophosphatemia
CSF pleocytosis (>50 × 10^6/L) In patients with an elevated CSF cell count, the differential diagnosis should be considered and excluded by appropriate testing	Infections, particularly due to cytomegalovirus, human immunodeficiency virus (HIV), Lyme disease, polio virus; inflammatory disorders (eg, transverse myelitis); infiltrative disorders (eg, leptomeningeal carcinomatosis or lymphomatosis)

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LEARNING OBJECTIVES AND CORE COMPETENCIES

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Neuro-oncology issue, participants will be able to:

- Recognize the evolving trends in molecular neuropathology and understand how they have become integral to modern tumor classification
- Describe clinical presentations, diagnosis, and management of patients with gliomas
- Describe the clinical presentation, diagnosis, biology, management, and prognosis of the most common pediatric brain tumors and neurocutaneous syndromes
- Understand the signs, symptoms, approach to diagnosis and staging, and treatment options for newly diagnosed, relapsed, and refractory primary and secondary central nervous system lymphoma
- Describe the presentation, diagnosis, treatment, and management of patients with central nervous system metastases, specifically brain parenchymal and leptomeningeal metastases
- Describe the presenting features, imaging characteristics, pathology, and management of tumors arising in or along the base of the skull
- Describe the initial evaluation to recognize, diagnose, and treat paraneoplastic neurologic disorders to achieve optimal oncologic and neurologic outcomes
- Identify the presenting signs and symptoms, pathophysiology, and management of the most common peripheral and central neurologic complications of chemotherapy, radiation therapy, and antiangiogenic therapy used for cancer treatment
- Describe common complications from cancer immunotherapy, including immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy, as well as their workup and management
- Describe the spectrum of complications experienced by patients with central nervous system malignancies including vasogenic edema, tumor-related epilepsy, venous thromboembolism, and endocrine and infectious disorders, and the best practices to minimize associated morbidity and mortality
- Summarize principles of palliative care for patients with central nervous system tumors including symptom management, support, and distress alleviation for care partners, transparent and empathetic communication, and timely and meaningful advance care planning

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Neuro-oncology issue covers the following core competencies:

- Patient Care and Procedural Skills
- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

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LIST OF ABBREVIATIONS

Neuro-oncology

AAN	American Academy of Neurology
ADL	Activities of daily living
ANNA-1	Antineuronal nuclear antibody type 1
ANNA-2	Antineuronal nuclear antibody type 2
ACTH	Adrenocorticotropic hormone
AGNA	Antiglial nuclear antibody
AIDP	Acute inflammatory demyelinating polyradiculoneuropathy
AIDS	Acquired immunodeficiency syndrome
ALK	ALK receptor tyrosine kinase
AMPA	α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
AQP4	Aquaporin-4
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CAR	Chimeric antigen receptor
CARTOX-10	CAR T-Cell Therapy–Associated Toxicity
CASPR2	Contactin-associated proteinlike 2
CBC	Complete blood count
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CIPN	Chemotherapy-induced peripheral neuropathy
CMT	Charcot-Marie-Tooth disease
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CRMP-5	Collapsin response mediator protein-5
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen 4
D2HG	D-2-hydroxyglutarate
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
DWI	Diffusion-weighted imaging
EANO	European Association of Neuro-oncology
ECG	Electrocardiogram
EEG	Electroencephalogram
EGFR	Epidermal growth factor receptor
EMG	Electromyography
ER	Extended release
ESMO	European Society for Medical Oncology
FAP	Familial adenomatous polyposis
FDA	US Food and Drug Administration
FDG-PET	Fludeoxyglucose positron emission tomography
FISH	Fluorescence in situ hybridization
FLAIR	Fluid-attenuated inversion recovery
GABA	γ-aminobutyric acid
$GABA_A$	γ-aminobutyric acid A
$GABA_B$	γ-aminobutyric acid B
GAD	Glutamic acid decarboxylase
GAD65	Glutamic acid decarboxylase 65
GBM	Glioblastoma
GFAP	Glial fibrillary acidic protein
GI	Gastrointestinal
H&E	Hematoxylin and eosin
βHCG	β-human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSV	Herpes simplex virus
HTLV	Human T-cell lymphotropic virus
ICANS	Immune effector cell–associated neurotoxicity syndrome
ICE	Immune Effector Cell–Associated Encephalopathy
ICI	Immune checkpoint inhibitor
IDH	Isocitrate dehydrogenase
IELSG32	International Extranodal Lymphoma Study Group-32
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgLON5	IgLON family member 5
IgM	Immunoglobulin M
IL-6	Interleukin-6
IM	Intramuscular
IV	Intravenous
IVIg	Intravenous immunoglobulin
KRAS	KRAS proto-oncogene, GTPase
LAM	Lymphangioleiomyomatosis
LGI1	Leucine-rich glioma inactivated protein 1
LZUP4	Leucine zipper 4
MAG	Myelin-associated glycoprotein
MAOI	Monoamine oxidase inhibitor
MAPK	Mitogen-activated protein kinase
MGUS	Monoclonal gammopathies of undetermined significance
MOG	Myelin oligodendrocyte glycoprotein
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
MuSK	Muscle-specific kinase
NF1	Neurofibromatosis type 1
NF2	*NF2*-related schwannomatosis
NIH	National Institutes of Health
NMDA	*N*-methyl-D-aspartate
NMOSD	Neuromyelitis optica spectrum disorder
NTRK	Neurotrophic tyrosine receptor kinase
OCT	Optical coherence tomography
PCA-1	Purkinje cell cytoplasmic antibody type 1
PCA-2	Purkinje cell cytoplasmic antibody type 2
PCP	Phenylcyclohexyl piperidine
PCR	Polymerase chain reaction
PD-1	Programmed cell death 1
PD-L1	Programmed death-ligand 1
PERM	Progressive encephalomyelitis with rigidity and myoclonus
PET	Positron emission tomography
PitNET	Pituitary neuroendocrine tumor
PLEX	Plasma exchange
PNS	Paraneoplastic
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes
PRECIS	Cranial Radiotherapy or Intensive Chemotherapy With Hematopoietic Stem Cell Rescue for Primary Central Nervous System Lymphoma in Young Patients
PRES	Posterior reversible encephalopathy syndrome
PROSPECT	Proactive Self-Management Program for Effects of Cancer Treatment
QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
QUARTZ	Quality of Life after Treatment for Brain Metastases
RANO	Response Assessment in Neuro-Oncology
REM	Rapid eye movement
RET	Ret proto-oncogene
RNA	Ribonucleic acid
ROS1	ROS proto-oncogene 1, receptor tyrosine kinase
RT	Radiation therapy
RYK	Receptor like tyrosine kinase
SCLC	Small cell lung cancer
SEGA	Subependymal giant cell astrocytoma
SHH	Sonic hedgehog
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
SMART	Strokelike migraine attacks after radiation therapy
SPECT	Single-photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitor
SV2A	Synaptic vesicle protein 2A
TSH	Thyroid-stimulating hormone
VEGF	Vascular endothelial growth factor
VTE	Venous thromboembolism
WHO	World Health Organization
WNT	Wingless and INT-1
WT	Wildtype

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NEURO-ONCOLOGY

ARTICLE 1: 2021 WORLD HEALTH ORGANIZATION CLASSIFICATION OF BRAIN TUMORS

David M. Meredith, MD, PhD; David J. Pisapia, MD. Continuum (Minneap Minn). December 2023; 29 (6 Neuro-oncology):1638–1661.

ABSTRACT

OBJECTIVE:

The classification of brain tumors is a rapidly evolving field that requires extensive integration of molecular diagnostic findings from an expanding set of platforms and assays. This article summarizes the schema presented in the 5th edition of the World Health Organization (WHO) classification of central nervous system (CNS) tumors while highlighting diagnostic molecular findings and discussing the strengths and weaknesses of commonly available testing modalities.

LATEST DEVELOPMENTS:

Several major changes in practice were introduced with the 5th edition of the CNS WHO classification, including molecular grading of adult diffuse gliomas, the introduction of many new entities within the spectrum of pediatric gliomas and glioneuronal tumors, and the widespread adoption of methylation classes as useful or even necessary diagnostic criteria. Additionally, several revisions to nomenclature (eg, *IDH*-mutant gliomas) were introduced for simplicity and to disambiguate from other tumor types.

ESSENTIAL POINTS:

The classification of brain tumors continues to grow in complexity alongside our improved understanding of their nuanced molecular underpinnings.

KEY POINTS

- **The majority of central nervous system (CNS) tumors possess highly characteristic genetic and epigenetic profiles, which are usually required to be integrated with histology for accurate classification.**
- **Single-gene tests, such as immunohistochemistry, fluorescence in situ hybridization, and polymerase chain reaction are rapid and cost-effective assays when a specific CNS tumor diagnosis or alteration is suspected.**
- **Comprehensive profiling of CNS tumors via chromosomal microarray or next-generation sequencing panels is frequently needed to resolve more complex differential considerations and to classify tumors with variable genetic profiles.**

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- Methylation profiling of CNS tumors has proven highly valuable for the creation of machine learning–based classifiers, and some tumor types cannot be accurately classified without obtaining a methylation profile.
- Adult diffuse gliomas are largely classified on the basis of *IDH1/2* and 1p/19q codeletion status, irrespective of microscopic appearance.
- A triple-variant immunohistochemical pattern (IDH1 R132H+, ATRX-, p53+) is highly specific for *IDH*-mutated astrocytomas, and formal demonstration of 1p/19q status is not necessary when present.
- Given the rate of false-positive 1p/19q codeletion results by fluorescence in situ hybridization, whole-arm testing of 1p and 19q via microarray or next-generation sequencing is recommended for oligodendrogliomas.
- Tumors lacking *IDH1/2* variations frequently show gain of chromosome 7, loss of chromosome 10, *TERT* promoter variation, or *EGFR* amplification. These features can also be used to diagnose glioblastomas in the absence of classic histology.
- Gliomas with histone H3 variations comprise a subset of highly aggressive tumors that occur in children and young adults. Diffuse midline gliomas carry variations or epigenetic dysregulation at K27, while diffuse hemispheric gliomas carry G34 variations.
- Pediatric low-grade diffuse gliomas often exhibit morphologic overlap with adult gliomas; however, they are much more indolent and contain unique driver mechanisms that often activate the MAPK pathway.
- Fusions involving *BRAF*, especially with the fusion partner *KIAA1549*, are highly characteristic of pilocytic astrocytomas. Alterations have also been described in other genes (eg, *NF1*, *FGFR1*, *BRAF*).
- Circumscribed gliomas are highly variable in behavior, ranging from benign (subependymal giant cell astrocytomas), to intermediate malignancy (chordoid gliomas, pleomorphic xanthoastrocytomas, astroblastomas), to highly aggressive (high-grade astrocytomas with piloid features).
- Similar to other pediatric low-grade gliomas, glioneuronal tumors exhibit a wide range of histologies and possess driver events, most commonly in the MAPK pathway.
- Ependymoma classification is based largely on the anatomic compartment (supratentorial, posterior fossa, and spine) and genetic and epigenetic profiles. While histologic grading is of limited utility, the posterior fossa A and *MYCN*-amplified spinal tumors are particularly aggressive.
- Molecular subclassification of medulloblastomas is paramount for prognosis and treatment planning. While wingless and INT-1 (WNT)-activated and sonic hedgehog (SHH)-activated groups can be classified with most next-generation sequencing panels, groups 3 and 4 (non-WNT, non-SHH) frequently require methylation profiling for accurate diagnosis.
- Although atypical teratoid/rhabdoid tumors can be easily diagnosed by light microscopy, three distinct transcriptional and methylation subgroups have been identified that may show distinct survival outcomes.
- Embryonal tumors with multilayered rosettes possess highly characteristic amplifications of a microRNA cluster on chromosome 19 (C19MC) that can only be detected by whole-genome array or next-generation sequencing platforms (including methylation arrays).
- Other recently described embryonal tumors such as CNS neuroblastomas or CNS tumors with *BCOR* internal tandem duplication may need methylation profiling to classify, given the lack of adequate coverage of their diagnostic genetic events on most available next-generation sequencing platforms.
- Despite long-established grading criteria for meningiomas, integration with cytogenetic and gene-variation data has shown significant improvement in predicting long-term behavior.
- Solitary fibrous tumors arising in the meninges are graded differently from non-CNS counterparts, considering only mitotic rate and the presence or absence of necrosis.
- Several new mesenchymal entities are recognized in the current WHO CNS tumor classification, including tumors with *FET::CREB* fusions, *DICER1* loss-of-function variations, and *CIC* rearrangements. While some are likely very aggressive, more data are needed to determine a precise WHO grade.

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ARTICLE 2: ADULT-TYPE DIFFUSE GLIOMAS

Macarena I. de la Fuente, MD. Continuum (Minneap Minn). December 2023;
29 (6 Neuro-oncology):1662–1679.

ABSTRACT

OBJECTIVE:

This article highlights key aspects of the diagnosis and management of adult-type diffuse gliomas, including glioblastomas and *IDH*-mutant gliomas relevant to the daily practice of the general neurologist.

LATEST DEVELOPMENTS:

The advances in molecular characterization of gliomas have translated into more accurate prognostication and tumor classification. Gliomas previously categorized by histological appearance solely as astrocytomas or oligodendrogliomas are now also defined by molecular features. Furthermore, ongoing clinical trials have incorporated these advances to tailor more effective treatments for specific glioma subtypes.

ESSENTIAL POINTS:

Despite recent insights into the molecular aspects of gliomas, these tumors remain incurable. Care for patients with these complex tumors requires a multidisciplinary team in which the general neurologist has an important role. Efforts focus on translating the latest data into more effective therapies that can prolong survival.

KEY POINTS

- Gliomas are relatively uncommon but are associated with significant morbidity and mortality.
- For certain glial tumor subtypes, targeted therapies have emerged as promising treatment options.
- Researchers have made progress in understanding and classifying gliomas, but there has been limited progress toward prolonging patient survival.
- Glioblastomas are one of the most aggressive solid tumors and the most common malignant primary central nervous system tumors.
- Therapeutic ionizing radiation is the only well-established risk factor for the development of glioblastomas.
- The clinical presentation of glioblastomas depends largely on tumor location and can include elevated intracranial pressure symptoms and seizures.
- MRI with contrast is the preferred imaging study when glioblastoma is suspected.
- MRI in patients with glioblastomas typically shows an infiltrative, heterogeneous, ring-enhancing lesion with central areas of necrosis on T1-weighted imaging with surrounding hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images.
- Molecular pathology is a key component of the integrated diagnosis of glioblastomas.
- The 2021 Society for Neuro-Oncology and European Association of Neuro-Oncology practice guideline update recommends against prescribing antiseizure medications to reduce the risk of seizures in patients with newly diagnosed brain tumors who have never had a seizure.
- Perioperative antiseizure medications are not recommended for patients with brain tumors who have never had a seizure.
- Surgical resection followed by adjuvant radiotherapy combined with chemotherapy should be considered in all patients with newly diagnosed glioblastoma.

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- Maximal safe resection is the recommended neurosurgical approach for glioblastomas. The extent of resection is associated with overall survival.
- Radiation therapy and temozolomide is the consensus best treatment for newly diagnosed glioblastomas after surgical resection or biopsy. The benefit of temozolomide is limited in patients with *MGMT* promoter unmethylated glioblastomas.
- Older patients with glioblastomas have a worse prognosis, and a hypofractionated course of radiation therapy with temozolomide, single-modality treatment, or supportive care may be considered.
- The identification of *IDH* variations in gliomas represents one of the major hallmarks in the field of neuro-oncology in recent decades, leading to significant progress in terms of glioma classification and prognosis and potential novel therapeutic approaches.
- Tumors with *IDH* variations accounted for 4.6% of all brain tumors and 12% of gliomas diagnosed in 2018.
- Histologic and molecular features are essential to confirm the diagnosis in *IDH*-mutant gliomas.
- Because the oncometabolite D-2 hydroxyglutarate (D2HG) accumulates in *IDH*-mutant tumors and can be detected and measured noninvasively through D2HG MR spectroscopy, this technique represents a valuable tool in clinical practice.
- The extent of surgical resection has a significant effect on the clinical outcomes for both low-grade and high-grade gliomas, particularly in *IDH*-mutant astrocytomas.
- Short-term radiation–induced toxicities include fatigue, headache, skin erythema, otitis, and alopecia.
- Long-term radiation–induced toxicities include radiation necrosis, cognitive decline, decreased health-related quality of life, and less commonly strokelike migraine attacks after radiation therapy.
- Vincristine-induced peripheral neuropathy is usually reversible, but improvement is gradual and may take many months.

ARTICLE 3: PEDIATRIC NEURO-ONCOLOGY

Fatema Malbari, MD. Continuum (Minneap Minn). December 2023;
29 (6 Neuro-oncology):1680–1709.

ABSTRACT

OBJECTIVE:

This article reviews the most common pediatric brain tumors, neurocutaneous syndromes, treatment-related neurotoxicities, and the long-term outcomes of survivors.

LATEST DEVELOPMENTS:

In the era of molecular diagnostics, the classification, management, and prognostication of pediatric brain tumors and neurocutaneous syndromes has been refined, resulting in advancements in patient management. Molecular diagnostics have been incorporated into the most recent World Health Organization 2021 classification. This knowledge has allowed for novel therapeutic approaches targeting the biology of these tumors with the intent to improve overall survival, decrease treatment-related morbidity, and improve quality of life. Advances in management have led to better survival, but mortality remains high and significant morbidity persists. Current clinical trials focus on tumor biology targeted therapy, deescalation of therapy, and multimodal intensified approaches with targeted therapy in more high-risk tumors.

ESSENTIAL POINTS:

Molecular diagnostics for pediatric brain tumors and neurocutaneous syndromes have led to novel therapeutic approaches targeting the biology of these tumors with the goals of improving

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overall survival and decreasing treatment-related morbidity. Further understanding will lead to continued refinement and improvement of tumor classification, management, and prognostication.

KEY POINTS

- Central nervous system (CNS) tumors are the most common solid tumors in children and young adults (ages 0 to 19 years) and are the leading cause of childhood (ages 0 to 14 years) cancer-related mortality.
- Although overall survival for patients with certain pediatric CNS tumors has improved, mortality remains high for patients with other tumors, and treatment-related and tumor-related morbidity persists.
- Pediatric gliomas are the most common pediatric CNS tumor, representing approximately 40% of all CNS tumors.
- Pediatric low-grade glioma molecular alterations involve the RAS-mitogen activated protein kinase pathway, most commonly involving *BRAF* (KIAA1549 fusion or V600E variation) or *NF1* germline variations.
- Management of pediatric low-grade gliomas is dependent on tumor location and characteristics and patient age.
- Neurocutaneous conditions, such as neurofibromatosis type 1 and tuberous sclerosis complex, are associated with an increased risk of developing pediatric low-grade gliomas.
- The revised diagnostic criteria for neurofibromatosis type 1 include confirmation of a heterozygous *NF1* deletion, a parent with neurofibromatosis type 1, and two or more choroidal anomalies.
- Pediatric high-grade gliomas (CNS World Health Organization grades 3 and 4) represent about 10% of pediatric CNS tumors and are the leading cause of cancer-related mortality in children younger than 19 years old, despite advances in management.
- Four different pediatric diffuse high-grade glioma groups have been defined in the World Health Organization 2021 classification: 1) diffuse midline glioma H3 K27-altered, 2) diffuse hemispheric glioma H3 G34-mutant, 3) diffuse pediatric-type high-grade glioma H3-wildtype and isocitrate dehydrogenase wildtype, and 4) infant-type hemispheric glioma.
- Management of pediatric high-grade gliomas includes maximal safe surgical resection followed by focal radiation therapy in children 3 years old or older.
- Genetic cancer predisposition syndromes associated with the development of pediatric high-grade gliomas include Li-Fraumeni syndrome, constitutional mismatch repair deficiency, and Lynch syndrome.
- Diffuse midline glioma of the pons remains an incurable diagnosis, with a median overall survival time of 11 months. Radiation therapy remains the standard treatment and can prolong life by an additional 3 to 4 months.
- Molecularly, there are four distinct medulloblastoma subgroups with different prognoses in the World Health Organization classification: wingless, sonic hedgehog, group 3, and group 4.
- The treatment of medulloblastomas is associated with considerable toxicity and can reduce quality of life. Cerebellar mutism syndrome after surgical resection has been reported in approximately 34% of patients.
- Cerebellar mutism syndrome is a poorly understood constellation of symptoms including emotional lability, paucity of speech, apraxia, and cerebellar and cranial nerve dysfunction, and is associated with neurocognitive impairment.
- Atypical teratoid/rhabdoid tumors are highly aggressive embryonal tumors that most commonly affect young children (11% and 4% of children with brain tumors younger than 1 year old and between 1 to 4 years old, respectively), with a 5-year overall survival rate of 30% to 40%.
- Recurrence rates in ependymomas are high and can be delayed, up to 15 years after initial therapy.
- Current treatment options for craniopharyngiomas include gross total resection or partial resection followed by focal radiation therapy. Both treatment options achieve comparable results and decrease the risk of tumor recurrence; however, both are associated with significant morbidity and reduced quality of life.
- Current standard treatment options for pediatric patients with brain tumors are associated with long-term neurologic toxicity and impaired quality of life.
- RT can cause acute and early-delayed neurotoxicity including headaches, pseudoprogression with

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worsening of preexisting neurologic symptoms, somnolence syndrome, and radiation necrosis, while late neurotoxicity includes radiation necrosis, neurocognitive impairment, vasculopathy, and secondary malignancies.

- Current recommendations for brain tumor survivors who have received RT include yearly neurologic examinations and brain MRI with diffusion-weighted imaging and MR angiography as clinically indicated.
- CNS tumor survivors should have yearly neuropsychological assessments to provide additional educational and school support as needed.
- Chimeric antigen receptor T-cell therapy for CNS brain tumors can be associated with neurotoxicity including immune effector cell–associated neurotoxicity syndrome or tumor inflammation–associated neurotoxicity.

ARTICLE 4: CENTRAL NERVOUS SYSTEM LYMPHOMA

Lauren Schaff, MD. Continuum (Minneap Minn). December 2023;
29 (6 Neuro-oncology):1710–1726.

ABSTRACT

OBJECTIVE:

This article reviews the clinical presentation, diagnostic workup, staging, and treatment of primary central nervous system (CNS) lymphoma and common manifestations of secondary CNS lymphoma.

LATEST DEVELOPMENTS:

Lymphoma can arise in the CNS de novo (primary CNS lymphoma) or as the result of systemic disease (secondary CNS lymphoma). Symptoms may include focal neurologic deficits related to the disease site, cognitive decline, and symptoms of increased intracranial pressure. Standard treatment may differ based on lymphoma subtype and location. A majority of CNS lymphoma is diffuse large B-cell subtype and exhibits aggressive behavior. First-line treatment is generally methotrexate-based polychemotherapy. Response rates to treatment are high, approximately 80% to 90% for primary CNS lymphoma, but relapse is common. Consolidation approaches including myeloablative chemotherapy followed by autologous stem cell rescue, nonmyeloablative chemotherapy, radiation, and medical maintenance regimens reduce rates of relapse. The recent development of targeted agents such as Bruton tyrosine kinase inhibitors and immunomodulatory strategies have shown promise in the treatment of CNS lymphoma. Immunotherapy in the form of checkpoint inhibitors and chimeric antigen receptor T cells is being studied. More indolent forms of lymphoma may be treated with radiation or targeted therapy.

ESSENTIAL POINTS:

CNS lymphoma is an uncommon but clinically meaningful manifestation of extranodal lymphoma. The diagnosis requires a high level of suspicion for rapid initiation of potentially curative treatment.

KEY POINTS

- Central nervous system (CNS) lymphoma involves the brain parenchyma, spinal cord, leptomeninges, dura, or vitreoretinal space without systemic involvement.
- The incidence of primary CNS lymphoma is increasing in immunocompetent patients more than 65 years old.

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- Systemic lymphoma involving the kidneys, adrenal glands, testes, paranasal sinuses, or retroperitoneal lymph nodes have a higher risk of CNS relapse.
- Patients with CNS lymphoma can present with focal neurologic deficits or nonspecific cognitive decline or behavioral changes.
- Twenty-five percent of patients with CNS lymphoma may have ocular involvement at diagnosis. Slit-lamp examination should be performed for all patients.
- Classic radiographic findings of CNS lymphoma include homogeneous enhancement in immunocompetent patients, minimal edema, and diffusion restriction.
- CNS lymphoma in immunocompromised patients can demonstrate a ring-enhancing pattern.
- If CNS lymphoma is on the differential diagnosis, steroids should be withheld before tissue sampling. Lymphotoxic effects can obscure pathology results.
- Aggressive surgical resection of CNS lymphoma is not associated with a survival benefit.
- Diffuse large B-cell lymphoma is the most common form of primary CNS lymphoma. Most primary CNS lymphomas are of the activated B-cell-like/nongerminal center subtype and are associated with mutations in the B-cell receptor pathway.
- Initiation of primary CNS lymphoma treatment is time-sensitive. Common practice is to begin treatment immediately after diagnosis, without an intervening hospital discharge.
- There are two phases of primary CNS lymphoma treatment: (1) induction and (2) consolidation or maintenance.
- Chemotherapeutic regimens used for systemic lymphoma generally have poor penetrance of the blood-brain barrier and are not effective for primary CNS lymphoma.
- Polychemotherapy regimens with a methotrexate backbone are first-line treatments for primary CNS lymphoma.
- Methotrexate is well tolerated and elicits responses in 80% to 90% of patients with CNS lymphoma. Tumor-directed treatment is recommended even in older patients.
- The role of intrathecal and intraocular chemotherapy as site-specific treatments for patients with lymphoma is controversial. These therapies may be reserved for methotrexate failure.
- In patients with primary CNS lymphoma, high-dose chemotherapy with thiotepa, busulfan, and cyclophosphamide followed by autologous stem cell rescue is the preferred consolidation strategy. Eligible patients are typically younger than 70 years and in good general health.
- Maintenance treatment may be a reasonable alternative to consolidation treatment for patients with primary CNS lymphoma.
- After primary CNS lymphoma treatment, patients should be monitored with imaging every 3 months for the first 2 years, then every 6 months for an additional 3 years, and then annually.
- Primary CNS lymphoma relapse occurs in up to 50% of patients.
- Rechallenge with methotrexate-based chemotherapy is reasonable for patients with relapse of primary CNS lymphoma who had an initial response to methotrexate that lasted 12 months or longer.
- Ibrutinib, a Bruton tyrosine kinase inhibitor, is highly effective in treating relapsed and refractory primary CNS lymphoma. It may be used in combination with other agents to prevent resistance.
- Secondary central nervous system involvement of systemic lymphoma can occur by hematologic spread, direct extension, or growth along neurovascular bundles.
- Methotrexate-based treatment is first-line therapy for secondary CNS diffuse large B-cell lymphoma.
- Patients with secondary CNS lymphoma may be eligible for chimeric antigen receptor T-cell therapy.
- CNS involvement of more indolent forms of B-cell lymphoma is rare, and it is often responsive to Bruton tyrosine kinase inhibition.
- CNS involvement of T-cell lymphomas is rare but confers a poor prognosis.
- Dural lymphoma is often indolent and may be treated with surgical resection or radiation with excellent response.
- Neurolymphomatosis often presents as a painful radiculopathy.
- Neurologic manifestations of intravascular lymphoma include strokes, peripheral neuropathy, and rapid-onset dementia. The diagnosis requires a biopsy.

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- Prognosis of CNS lymphoma has improved over the last few decades with widespread adoption of methotrexate-based therapy.
- Cognitive deficits and issues affecting quality of life are of increasing importance as survival in CNS lymphoma improves.

ARTICLE 5: BRAIN METASTASES AND LEPTOMENINGEAL DISEASE

Priya Kumthekar, MD; Emilie Le Rhun, MD. Continuum (Minneap Minn). December 2023; 29 (6 Neuro-oncology):1727–1751.

ABSTRACT

OBJECTIVE:

Central nervous system (CNS) metastases include brain parenchymal, spinal cord, and leptomeningeal metastases. This article discusses the diagnostic and therapeutic advances of the last decade that have improved outcomes for patients with these CNS metastases.

LATEST DEVELOPMENTS:

The diagnostic tools for CNS metastases, particularly leptomeningeal disease, have evolved over the past decade with respect to advancements in CSF analysis. Multiple medical therapies are now available for brain metastasis treatment that have shown CNS efficacy, including targeted therapies and antibody-drug conjugates. Molecular testing for CNS metastases has become more common and the repertoire of molecularly targeted therapies continues to expand. Advancements in radiation therapy, including improvements in stereotactic radiation techniques, whole-brain radiation with hippocampal avoidance, and proton beam radiation, have changed the radiation management of patients with CNS metastases. New intrathecal agents are currently being tested for the management of leptomeningeal metastases.

ESSENTIAL POINTS:

CNS metastases are far more common than primary brain tumors and are increasing in prevalence in the setting of improved treatments and prolonged survival in patients with systemic cancers. There have been many changes in the diagnostics and treatment of CNS metastases, yielding subsequent improvements in patient outcomes with further advancements on the horizon.

KEY POINTS

- With improvements in systemic cancer therapies, patients are living longer and the prevalence of brain metastases is rising.
- Central nervous system (CNS) metastases from systemic cancers are more common than primary brain tumors and may occur within the brain and spinal cord parenchyma, leptomeninges, or the dura.
- The anatomic difference between dural, brain parenchymal, and leptomeningeal metastases should be distinguished since this impacts treatment decision making.
- The optimal imaging modality for brain metastasis imaging is brain MRI with and without contrast.
- Brain metastases most commonly associated with hemorrhage include melanoma, renal cell and thyroid carcinomas, and choriocarcinoma.
- The management of brain metastases may include a combination of surgery, radiation, or medical therapy, and ideally treatment decision making should involve a multidisciplinary clinical team of physicians.
- Surgery may be indicated for brain metastases, particularly for solitary or symptomatic tumors.

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- When brain metastasis tissue is available, molecular testing should be considered since its molecular profile could vary from the primary cancer site.
- Stereotactic radiosurgery has become the mainstay for the treatment of brain metastases and is typically preferred over whole-brain radiation therapy when possible.
- Whole-brain radiotherapy with hippocampal avoidance has been shown to be less detrimental to patients' cognition in comparison to traditional whole-brain radiotherapy.
- Novel molecularly targeted agents and antibody-drug conjugates that cross the blood-brain barrier are available for CNS metastases, particularly for *HER2*-positive and harbor epidermal growth factor receptor genetic variations.
- Spinal cord compression can be a complication of CNS or vertebral metastases and is considered a neurologic emergency.
- The diagnosis of leptomeningeal disease is definitively confirmed by positive CSF cytology for malignant cells, although the sensitivity of this test is only about 50% to 70% for the initial CSF sampling.
- Novel diagnostics including CSF circulating tumor cells and tumoral DNA are being investigated as next-generation diagnostic tools for leptomeningeal disease.
- In specific clinical scenarios, intrathecal therapy can be considered for the treatment of leptomeningeal disease.
- In a prospective randomized clinical trial, proton beam craniospinal irradiation has been shown to improve survival in patients with leptomeningeal disease as opposed to traditional photon beam radiation therapy.
- Health care disparities should be considered in the setting of CNS metastases, particularly with respect to the availability of stereotactic radiosurgery and proton beam radiation.

ARTICLE 6: SKULL BASE TUMORS

Deborah A. Forst, MD; Pamela S. Jones, MD, MS, MPH. Continuum (Minneap Minn). December 2023; 29 (6 Neuro-oncology):1752–1778.

ABSTRACT

OBJECTIVE:

This article reviews the presenting features, molecular characteristics, diagnosis, and management of selected skull base tumors, including meningiomas, vestibular schwannomas, pituitary neuroendocrine tumors, craniopharyngiomas, chordomas, ecchordosis physaliphora, chondrosarcomas, esthesioneuroblastomas, and paragangliomas.

LATEST DEVELOPMENTS:

Skull base tumors pose a management challenge given their complex location and, as a result, the tumors and treatment can result in significant morbidity. In most cases, surgery, radiation therapy, or both yield high rates of disease control, but the use of these therapies may be limited by the surgical accessibility of these tumors and their proximity to critical structures. The World Health Organization classification of pituitary neuroendocrine tumors was updated in 2022. Scientific advances have led to an enhanced understanding of the genetic drivers of many types of skull base tumors and have revealed several potentially targetable genetic alterations. This information is being leveraged in the design of ongoing clinical trials, with the hope of rendering these challenging tumors treatable through less invasive and morbid measures.

ESSENTIAL POINTS:

Tumors involving the skull base are heterogeneous and may arise from bony structures, cranial nerves, the meninges, the sinonasal tract, the pituitary gland, or embryonic tissues. Treatment often requires a multidisciplinary approach, with participation from radiation oncologists,

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medical oncologists, neuro-oncologists, and surgical specialists, including neurosurgeons, otolaryngologists, and head and neck surgeons. Treatment has largely centered around surgical resection, when feasible, and the use of first-line or salvage radiation therapy, with chemotherapy, targeted therapy, or both considered in selected settings. Our growing understanding of the molecular drivers of these diseases may facilitate future expansion of pharmacologic options to treat skull base tumors.

KEY POINTS

- Although many meningiomas are found incidentally through head imaging performed for other reasons, patients may present with headaches, seizures, vision changes, personality changes, loss of hearing, weakness, or difficulty with speech or swallowing.
- Grade 1 meningiomas of the skull base are enriched with specific driver genetic variations, notably *SMO* in olfactory groove meningiomas, as well as *PI3K*, *AKT*, *TRAF7*, and *POLR2A*.
- Meta-analysis has shown that endoscopic technique does not offer a significant advantage over open craniotomy in the resection of meningioma, and it may have higher rates of subtotal resection and postoperative CSF leak.
- Patients with vestibular schwannomas most commonly present with unilateral sensorineural hearing loss and tinnitus and less frequently present with vertigo and imbalance. Patients with larger tumors may develop symptoms related to brainstem compression or hydrocephalus.
- For vestibular schwannomas smaller than 3 cm, some studies suggest stereotactic radiosurgery may be superior to surgery for hearing and facial function preservation, whereas other studies show that longer-term rates of hearing preservation may be similar between stereotactic radiosurgery and microsurgery.
- Incidentally discovered nonfunctioning pituitary adenomas may be found in up to 10% of brain MRI studies.
- Studies have found that standard metrics like Ki-67 do not adequately predict pituitary neuroendocrine tumor reoccurrence or invasiveness.
- Pituitary neuroendocrine tumors that undergo gross total resection as gauged by MRI have a 10% risk of reoccurrence at 5years, so serial imaging is recommended.
- Given the prevalence of *BRAF*^{V600E} variations in papillary craniopharyngiomas, BRAF/MEK inhibitor therapy (eg, with vemurafenib and cobimetinib) is being tested in clinical studies, with preliminary results demonstrating high rates of treatment response.
- Brachyury expression is a marker found distinctively in chordomas and can be used to pathologically distinguish them from similar appearing tumors like chondrosarcomas.
- Targeted therapy of chordomas with tyrosine kinase inhibitors and agents inhibiting the PI3K-mTOR pathway have been studied with some favorable results, although larger studies are needed.
- Since ecchordosis physaliphora cannot be reliably distinguished from chordoma by histopathologic features alone, the diagnosis hinges on the identification of common radiographic characteristics.
- Genomic testing is commonly performed for chondrosarcomas because *IDH1* and *IDH2* variations are associated with longer progression-free and metastasis-free survival in high-grade chondrosarcomas.
- Up to 22% of patients with esthesioneuroblastomas may additionally have cervical lymphadenopathy at presentation, representing nodal metastases.
- Limited sequencing data shows a broad range of genetic alterations among esthesioneuroblastoma samples, although recurrent variations are not commonly observed. The most frequently observed are *TP53* alterations, with recent studies suggesting potentially targetable alterations in the mTOR, CDK, and growth factor signaling pathways.
- There are early reports of efficacy using peptide receptor radionuclide therapy (eg, lutetium Lu 177 dotatate) to treat patients with advanced disease, taking advantage of esthesioneuroblastomas' somatostatin receptor overexpression as a molecular target.
- In adults, between 30% and 40% of paragangliomas are familial or hereditary, with pathologic germline variations identified in at least 17 genes to date; therefore, the evaluation of patients with paragangliomas should include a detailed family history and referral to a genetic counselor to discuss testing for a heritable genetic variation.

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ARTICLE 7: PARANEOPLASTIC NEUROLOGIC SYNDROMES

Jerome J. Graber, MD, MPH, FAAN. Continuum (Minneap Minn). December 2023; 29 (6 Neuro-oncology):1779–1808.

ABSTRACT

OBJECTIVE:

Progress is ongoing in understanding paraneoplastic neurologic disorders, with new syndromes and antibodies being described and more detailed evidence available to guide workup for diagnosis and treatment to improve outcomes. Many excellent reviews have summarized the molecular features of different antibodies, but this article emphasizes the clinical features of each syndrome that may help guide initial diagnosis and treatment, which often should occur before an antibody or cancer is found to confirm the diagnosis.

LATEST DEVELOPMENTS:

Recent findings include updated diagnostic criteria with validated sensitivity and specificity, discovery of novel antibodies, and clinical findings that increase the likelihood of an underlying paraneoplastic disorder. Suggestive syndromes that have been recently identified include faciobrachial dystonic seizures and pilomotor auras in anti–leucine-rich glioma inactivated protein 1 encephalitis, extreme delta brush on EEG in *N*-methyl-D-aspartate (NMDA)-receptor encephalitis, déjà vu aura in anti–glutamic acid decarboxylase 65 (GAD65) encephalitis, and sleep disturbances in several disorders. In addition, there is confirmed utility of brain positron emission tomography (PET) and CSF markers, including carcinoembryonic antigen and oligoclonal bands, as well as improved tests for the presence of leptomeningeal cancer cells in CSF. Associations of cancer immunotherapies with paraneoplastic syndromes and herpes simplex virus encephalitis (and COVID-19) with NMDA-receptor encephalitis have been described.

ESSENTIAL POINTS:

All neurologists should be aware of advances regarding paraneoplastic neurologic syndromes, as patients can present with a wide variety of neurologic symptoms and earlier diagnosis and treatment can improve outcomes.

KEY POINTS

- Although various antibodies may cause overlapping or different clinical presentations, some paraneoplastic syndromes will not have an associated detectable antibody.
- CSF 14-3-3 protein is a nonspecific marker of neuronal injury and can be positive in prion diseases or paraneoplastic neurologic disorders.
- Ictal autonomic symptoms like gastrointestinal changes, piloerection, ictal fever, bladder sensations, or cough may be more common in antibody-associated epilepsies.
- Including the brain in positron emission tomography (PET) screening of the body for occult cancers can help diagnose paraneoplastic neurologic syndromes (eg, showing focal brain hypermetabolism).
- Psychiatric and sleep disturbances, including suicidal thoughts or attempts, are common in anti–*N*-methyl-D-aspartate (NMDA)-receptor encephalitis.
- Up to 25% of patients with herpes simplex virus encephalitis may develop autoimmune encephalitis (mostly anti-NMDA-receptor) within 4 months, with antibodies preceding clinical onset.
- Focal faciobrachial dystonic or pilomotor seizures are a suggestive feature of anti–leucine-rich glioma inactivated protein 1 antibody–associated syndromes.

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- Automatisms and impaired consciousness are much more common in glutamic acid decarboxylase 65 (GAD65)-associated epilepsy compared with other autoimmune epilepsies.
- Persistent neuropsychiatric symptoms are common after treatment of autoimmune encephalitis and require ongoing symptomatic support.
- Anti–aquaporin-4 antibodies are associated with cancer in 5% of cases, especially in men more than 50years old with intractable vomiting.
- Patients with anti–glutamic acid decarboxylase 65 (GAD65) antibodies can have varying associated syndromes (eg, epilepsy, cerebellar syndromes, diabetes) over their lifetimes.
- Downbeat nystagmus (especially when vibration-induced) is suggestive of a paraneoplastic cause of cerebellar ataxia.
- Diabetes is common in patients with stiff person syndrome, so patients should have appropriate screening, especially before using corticosteroids or high-glucose immunoglobulin therapy.
- Up to 20% of patients with immune checkpoint inhibitor–associated myasthenia gravis may have concurrent myositis and myocarditis.
- In patients with dermatomyositis, amyopathic or male patients, those with rapid progression, dysphagia, high creatine kinase levels, antibodies against nuclear matrix protein 2, melanoma differentiation-associated protein 5, or transcription intermediary factor-γ, or "honeycomb" MRI changes in the quadriceps muscles are associated with increased risk of malignancy.

ARTICLE 8: NEUROLOGIC COMPLICATIONS OF CONVENTIONAL CHEMOTHERAPY AND RADIATION THERAPY

Jennie W. Taylor, MD, MPH. Continuum (Minneap Minn). December 2023; 29 (6 Neuro-oncology):1809–1826.

ABSTRACT

OBJECTIVE:

Neurologic complications are among the most common and feared outcomes of cancer treatments. This review discusses the signs and symptoms, mechanisms, and management of the most common peripheral and central neurologic complications of chemotherapy, radiation therapy, and antiangiogenic therapy during cancer treatment and in survivors.

LATEST DEVELOPMENTS:

The landscape of cancer treatments is evolving to include more targeted and biologic therapies, in addition to more traditional cytotoxic therapies and radiation therapy. With increasingly complex regimens and longer survival for patients with cancer, the early recognition and management of neurologic complications is key to improving the morbidity and mortality of patients living with cancer.

ESSENTIAL POINTS:

Neurologists should be familiar with acute central and peripheral toxicities that can occur during cancer treatment and delayed toxicities that can occur years after exposure. Neurologists should be familiar with the clinical and radiologic presentations of these complications and strategies for management.

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KEY POINTS

- The Common Terminology Criteria for Adverse Events is a widely accepted grading system for assessing adverse events caused by cancer treatments. Neurologists should be familiar with the grading system for neurologic complications when coordinating care for patients with cancer.
- Acute central neurologic toxicities associated with chemotherapy require heightened awareness for early detection and management to minimize neurologic morbidity.
- Acute central neurologic toxicities are seen more commonly with high doses of cytotoxic agents, prior radiation exposure, intrathecal administration, and comorbid renal and hepatic dysfunction.
- Vincristine may cause a severe neuropathy in patients with Charcot-Marie-Tooth disease type 1A which may resemble Guillain-Barré syndrome and this agent should be avoided in these patients.
- Chemotherapy-induced peripheral neuropathy occurs most frequently within the first 2 months of treatment and is usually dose dependent, and early recognition is key as treatment dose and frequency adjustments can minimize the impact on cancer survivors.
- Effective treatments for pain associated with chemotherapy-induced peripheral neuropathy include duloxetine, tricyclic antidepressants, antiseizure medications, and topical and nonpharmacologic approaches.
- Neurologists should be able to recognize the cerebrovascular complications of antiangiogenic therapy and radiation therapy to minimize morbidity and mortality from cancer treatment.
- Risk factors for developing cancer-related cognitive impairment include lower cognitive reserve, anxiety and depression, fatigue, exposure to radiation, and the specifics of certain treatments.
- Factors that increase the risk of developing toxicity from radiation therapy include a larger volume of normal brain in the radiation field and a higher total radiation dose given over fewer fractions.
- Pseudoprogression is often seen within 6 months of radiation therapy, in the early-delayed phase, and can occur in up to 30% of high-grade cancers treated concurrently with intensity-modulated radiation therapy and temozolomide.
- Radiation necrosis is a long-term complication of radiation therapy that may occur several years after exposure and can resemble tumor recurrence. It may be effectively treated with bevacizumab.
- Strokelike migraine attacks after radiation therapy (SMART) syndrome is a delayed neurologic complication that often manifests as focal seizures and can be difficult to distinguish from tumor recurrence.
- Fasciculation potentials and myokymic discharges seen on EMG favor a diagnosis of radiation-induced versus neoplastic plexopathy.

ARTICLE 9: NEUROLOGIC COMPLICATIONS OF CANCER IMMUNOTHERAPY

Nancy Wang, MD, MPH. Continuum (Minneap Minn). December 2023; 29 (6 Neuro-oncology):1827–1843.

ABSTRACT

OBJECTIVE:

Immunotherapeutic approaches have revolutionized cancer treatment with immune checkpoint inhibitors and adoptive T-cell therapy now approved to treat a variety of solid and hematologic malignancies. This article summarizes the distinctive neurologic side effects of these therapies as well as their management.

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LATEST DEVELOPMENTS:

Neurologic immune-related adverse events are rare but potentially serious complications of immune checkpoint inhibitors. Both peripheral and central nervous system disorders have been described, often necessitating a pause or cessation of immunotherapy. Immune effector cell–associated neurotoxicity syndrome is a potentially serious complication of chimeric antigen receptor T-cell therapy. While symptoms may be mild and self-limited, delirium, encephalopathy, seizures, focal neurologic deficits, and fulminant cerebral edema can be seen. Close neurologic monitoring is imperative. The mainstay of treatment for neurologic complications includes high-dose corticosteroids, although other immunomodulatory strategies may be used in severe or refractory cases.

ESSENTIAL POINTS:

The spectrum of neurologic complications of cancer immunotherapy is broad, encompassing both central and peripheral nervous system disorders, indolent as well as fulminant clinical presentations, and wide-ranging severity with variable response to treatment. Early identification and multidisciplinary management are crucial to balance neurologic recovery and antitumor control.

KEY POINTS

- Neurologic immune-related adverse effects can affect both the central and peripheral nervous systems, although peripheral complications are more common.
- The incidence of neurologic immune-related adverse effects is higher for combined anti–cytotoxic T-lymphocyte antigen 4 and anti–programmed cell death 1 or programmed death-ligand 1 therapy than monotherapy.
- Neurologic complications of immune checkpoint inhibitors tend to arise within the first 6 months of treatment.
- The presence of one immune-related adverse event or neurologic immune-related adverse effect should prompt evaluation for overlapping syndromes, such as myositis and myocarditis.
- Myopathy and myasthenia gravis are two common peripheral nervous system complications of immune checkpoint inhibitors. While response to steroids and other therapies is typically favorable, associated mortality rates are as high as 20% to 30%.
- In contrast to chemotherapy-induced neuropathy, immune checkpoint inhibitor-related neuropathies are more often acute or subacute in onset and non–length dependent in distribution.
- Encephalitis and meningitis are the two most common central nervous system complications of immune checkpoint inhibitors, which should be distinguished from infectious causes.
- Autoimmune antibodies are elevated in up to one-half of patients with immune checkpoint inhibitor–related encephalitis. However, interpretation should be made in the appropriate clinical context given the possibility of nonpathogenic antibodies and paraneoplastic disorders.
- Immune effector cell–associated neurotoxicity syndrome (ICANS), previously known as *cytokine release encephalopathy syndrome*, can occur in up to 50% of patients treated with chimeric antigen receptor (CAR) T-cell therapy.
- Immune effector cell–associated neurotoxicity syndrome (ICANS) is associated with earlier onset and higher severity of cytokine release syndrome. The presentation is biphasic with the first peak within 5 days of chimeric antigen receptor (CAR) T-cell administration, often occurring with cytokine release syndrome, and a second delayed peak occurring 3 to 4 weeks later.
- The immune effector cell–associated neurotoxicity syndrome (ICANS) grade is used to assess the severity of neurologic symptoms. Neuroimaging should be performed in patients with grade 2 or higher ICANS.
- Long-term neurologic effects after chimeric antigen receptor (CAR) T-cell therapy are now being described and include cerebrovascular complications, neuropsychiatric disturbances, and movement disorders.
- The mainstay of managing immune effector cell–associated neurotoxicity syndrome (ICANS) consists of

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high-dose corticosteroids such as dexamethasone. While interleukin-6 directed with tocilizumab may be indicated for cytokine release syndrome, it is generally not effective for the treatment of ICANS.

- It remains uncertain whether all patients undergoing chimeric antigen receptor (CAR) T-cell therapy should receive a prophylactic antiseizure medication. Levetiracetam is widely used due to its favorable side effect profile and minimal drug interactions.

ARTICLE 10: MANAGEMENT OF COMPLICATIONS IN NEURO-ONCOLOGY PATIENTS

Mary R. Welch, MD, MS. Continuum (Minneap Minn). December 2023;
29 (6 Neuro-oncology):1844–1871.

ABSTRACT

OBJECTIVE:

The purpose of this article is to familiarize the reader with the spectrum of neurologic and medical complications relevant to the care of patients with neurologic cancer while highlighting best practices to prevent morbidity and mortality. Topics include tumor-related epilepsy, vasogenic edema, complications of corticosteroid use, disruption of the hypothalamic-pituitary axis, venous thromboembolism, and opportunistic infection.

LATEST DEVELOPMENTS:

In 2021, a joint guideline from the Society for Neuro-Oncology and the European Association of Neuro-Oncology reaffirmed recommendations first established in 2000 that patients with newly diagnosed brain tumors should not be prescribed an antiseizure medication prophylactically. For those with tumor-related epilepsy, monotherapy with a non–enzyme-inducing anticonvulsant is the preferred initial treatment, and levetiracetam remains the preferred first choice. Surveys of physician practice continue to demonstrate excessive use of glucocorticoids in the management of patients with both primary and metastatic central nervous system malignancy. This is particularly concerning among patients who require checkpoint inhibitors as the efficacy of these agents is blunted by concomitant glucocorticoid use, resulting in a reduction in overall survival. Finally, direct oral anticoagulants have been shown to be safe in patients with brain tumors and are now favored as first-line treatment among those who require treatment for venous thromboembolism.

ESSENTIAL POINTS:

Medical care for patients impacted by primary and secondary central nervous system malignancy is complex and requires a committed team-based approach that routinely calls upon the expertise of physicians across multiple fields. Neurologists have an important role to play and should be familiar with the spectrum of complications impacting these patients as well as the latest recommendations for management.

KEY POINTS

- Given the projected rise in global cancer burden over the next 2 decades, clinicians are increasingly likely to encounter patients with neurologic cancer in routine practice.
- Patients with gliomas whose tumors carry a variation in the isocitrate dehydrogenase gene are at a

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particularly high risk of seizures, possibly due to the accumulation of 2-hydroxyglutarate, a byproduct of the genetic variant with neuroexcitatory properties.

- Tumor-directed therapies, including the oral chemotherapy agent temozolomide as well as radiation therapy, have been shown to reduce seizure frequency among patients with primary central nervous system malignancy.
- Among patients with low-grade gliomas, consistent use of single-agent temozolomide can allow for the reduction or even discontinuation of antiseizure medications.
- Clinicians should not prescribe antiseizure medications to patients with newly diagnosed brain tumors who have not had a seizure.
- Patients with central nervous system malignancy who experience a seizure, either partial or generalized, are at high risk of another event and should be on antiseizure medication.
- Levetiracetam remains the usual first-choice antiseizure medication for patients with neurologic cancer based on its overall tolerability, lack of drug-drug interactions, affordability, rapid onset, availability in multiple formulations, and ease of titration.
- Up to 10% of patients taking levetiracetam experience adverse effects—typically fatigue, nervousness, and irritability—that can impact adherence and quality of life.
- Vasogenic edema in patients with neurologic cancer is a direct consequence of blood-brain barrier disruption, either by rapidly dividing malignant cells, the impact of ionizing radiation, or some combination of the two.
- Increased intracranial pressure can present with headache, imbalance, blurred vision, transient confusion, and drop attacks with preserved consciousness.
- Synthetic glucocorticoids are a highly effective first-line treatment for symptomatic vasogenic edema, capable of rapidly ameliorating symptoms and restoring neurologic function.
- For most patients with symptomatic vasogenic edema, 4 mg of dexamethasone per day is more than sufficient; higher doses are rarely warranted.
- Among those not on routine prophylaxis, the diagnosis of *P. jirovecii* pneumonia should be considered in any patient with cancer who is on combined immunosuppressive therapy or has other risk factors and reports dyspnea and dry cough.
- Bevacizumab is a monoclonal antibody that plays an important role in the management of patients with neurologic cancer and symptomatic edema, primarily as a steroid-sparing agent.
- Bevacizumab effectively restores the blood-brain barrier, accounting for its profound antiedema effect as well as the characteristic imaging changes that accompany its use.
- Excessive use of glucocorticoids can have a negative impact on overall survival, particularly among patients treated with checkpoint inhibitors.
- The use of steroids in the management of vasogenic edema for patients with central nervous system malignancy should be individualized, clinically based, and judicious.
- It is important to counsel patients and caregivers about the possibility of clinical worsening in the setting of steroid dose reduction.
- Hypophysitis impacts 5% to 17% of patients treated with the anticytotoxic T-lymphocyte–associated antigen 4 agent ipilimumab.
- Patients with primary central nervous system malignancy are at particularly high risk of venous thromboembolism, with some studies suggesting that up to one-third of patients are affected.
- Direct oral anticoagulants have been shown to be safe in patients with brain tumors and are now favored as a first-line treatment among patients who require treatment for venous thromboembolism.
- Inferior vena cava filters should only be deployed in patients who have strict contraindications to anticoagulation and life-threatening thrombus burden.

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ARTICLE 11: PALLIATIVE CARE AND CARE PARTNER SUPPORT IN NEURO-ONCOLOGY

Akanksha Sharma, MD. Continuum (Minneap Minn). December 2023;
29 (6 Neuro-oncology):1872–1895.

ABSTRACT

The journey for a patient with a brain tumor and their loved ones can be extremely challenging due to the high burden of physical symptoms and the emotional distress caused by the diagnosis. Optimizing quality of life by addressing symptoms and reducing this emotional distress can improve treatment tolerance and outcomes and alleviate care partner distress and burden. Symptoms in patients with central nervous system (CNS) tumors can vary in onset and intensity, ranging from headaches, seizures, and focal weakness to emotional distress and cognitive dysfunction. Additionally, care partners may demonstrate distress due to the high burden of care and need appropriate support structures and access to resources to alleviate this stress. Evidence-based recommendations are unfortunately limited given the lack of high-quality research in this area, but patients living with CNS tumors and their loved ones can benefit from early and routine symptom identification and management, compassionate and transparent communication, and practical guidance for the future. These principles are part of palliative care, a field of medicine focused on alleviating suffering in patients with serious, chronic illness. Clinicians involved in the care of patients with CNS tumors must be educated in these important primary palliative care principles. This article focuses on key symptom management, strategies for high-quality communication, a discussion of advance care planning, and an overview of end-of-life care.

KEY POINTS

- Palliative care, a person-centered approach that aims to alleviate suffering and improve the quality of life of patients with serious illness and their care partners, should be an integral part of care for patients with central nervous system (CNS) tumors.
- Care partners of patients with CNS tumors carry a high burden and may be impacted emotionally, physically, socially, and financially. They benefit from being actively engaged by the care team, receiving education and support, and being directed to resources as and when needed.
- Headaches in patients with CNS tumors can have many contributing factors and a careful history is needed to help develop the most appropriate plan of care.
- Dexamethasone should only be used when the headache is attributed to edema or mass effect, and to avoid toxicity it should be used at the lowest required dose for the shortest possible amount of time.
- Patients with CNS tumors and their care partners report a high burden of anxiety and distress which can severely impact quality of life, but this area remains under-researched and management is extrapolated from the general population of patients with cancer.
- Existential distress is also a prevalent symptom in patients with brain tumors and can be very troubling. Despite limited treatment options, this distress should be validated and referral for psychological interventions should be considered.
- Psychiatric symptoms ranging from anhedonia and disinhibition to agitation or mania may present during the CNS tumor disease course and may be managed with sedatives or antipsychotics.
- Poor sleep quality is a common symptom in patients with CNS tumors with a direct impact on overall

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well-being. Optimization requires addressing potential contributing factors and considering both nonpharmacologic and pharmacologic interventions.

- Fatigue is a common and often debilitating symptom in patients with CNS tumors with multiple contributing factors that require careful assessment and optimization, including addressing medication side effects, improving sleep, laboratory workup, and increasing activity levels when possible.
- Constipation can occur as a side effect of CNS tumor medications or secondary to diet and can be quite uncomfortable without early, effective management.
- Diarrhea in a patient on immunotherapy should prompt a work-up for colitis prior to initiating antidiarrheal therapy.
- Cognitive dysfunction is a common symptom in patients with brain tumors. Radiation therapy is a significant contributor, although recent findings have helped to reduce radiation neurotoxicity.
- Numerous studies have demonstrated the benefit of inpatient rehabilitation for patients with brain tumors, with good functional outcomes and the ability to return home.
- Focal limb weakness in patients with CNS tumors can significantly limit a patient's independence, increase care needs, and increase their risk for venous thrombosis or embolism.
- Swallowing difficulties in patients with CNS tumors may come to attention long after onset when they have become severe enough to cause aspiration and complications.
- Gait impairment in patients with CNS tumors can be very limiting for the patient and increase their dependence on care partners and should be addressed with early and aggressive physical therapy and appropriate arrangement of assistive devices.
- Incontinence is a physically and emotionally challenging symptom for patients with CNS tumors and their care partners; feelings around this topic should be explored and validated, and support should be provided in the form of education and training.
- Communicating with seriously ill patients with CNS tumors and their care partners requires a nuanced approach, balancing hope, compassion, and honesty. Information needs and preferences should be elicited and respected and conversations should focus on hoping for the best while also preparing for all possible outcomes.
- Planning for the future includes an understanding of one's prognosis, but a level of comfort and trust has to be built prior to having this discussion and all parties involved must understand the significant uncertainty inherent in CNS tumor prognostication.
- Advance care planning for patients with CNS tumors can be helpful when it encourages the patient to think about acceptable quality of life and limits on medical interventions and helps clarify hopes and goals for the future.
- It is best to avoid phrases such as "withdrawal of care" or "stopping all treatment," choosing instead to highlight active interventions like "focusing on managing symptoms" and "ensuring patient comfort."

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Issue Overview

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Continuum: Lifelong Learning in Neurology® is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills.

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Neuro-oncology issue, participants will be able to:

- Recognize the evolving trends in molecular neuropathology and understand how they have become integral to modern tumor classification
- Describe clinical presentations, diagnosis, and management of patients with gliomas
- Describe the clinical presentation, diagnosis, biology, management, and prognosis of the most common pediatric brain tumors and neurocutaneous syndromes
- Understand the signs, symptoms, approach to diagnosis and staging, and treatment options for newly diagnosed, relapsed, and refractory primary and secondary central nervous system lymphoma
- Describe the presentation, diagnosis, treatment, and management of patients with CNS metastases, specifically brain parenchymal and leptomeningeal metastases
- Describe the presenting features, imaging characteristics, pathology, and management of tumors arising in or along the base of the skull
- Describe the initial evaluation to recognize, diagnose, and treat paraneoplastic neurologic disorders to achieve optimal oncologic and neurologic outcomes
- Identify the presenting signs and symptoms, pathophysiology, and management of the most common peripheral and central neurologic complications of chemotherapy, radiation therapy, and antiangiogenic therapy used for cancer treatment
- Describe common complications from cancer immunotherapy, including immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy, as well as their workup and management
- Describe the spectrum of complications experienced by patients with central nervous system malignancies including vasogenic edema, tumor-related epilepsy, venous thromboembolism, and endocrine and infectious disorders, and the best practices to minimize associated morbidity and mortality
- Summarize principles of palliative care for patients with central nervous system tumors including symptom management, support, and distress alleviation for care partners, transparent and empathetic communication, and timely and meaningful advance care planning

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Neuro-oncology issue covers the following core competencies:

- Patient Care and Procedural Skills

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- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

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Unlabeled Use of Products/Investigational Use Disclosure: Dr de la Fuente discusses the unlabeled/investigational use of vorasidenib in clinical trials for the treatment of brain tumors.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Graber discusses the unlabeled/investigational use of corticosteroids, cyclophosphamide, intravenous immunoglobulin, ixazomib, lenalidomide, plasma exchange, and rituximab for the treatment of paraneoplastic neurologic syndromes.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Schaff discusses the unlabeled/investigational use of chimeric antigen receptor T-cell therapy, ibrutinib, immune checkpoint inhibitors, lenalidomide, and temozolomide for the treatment of primary central nervous system lymphoma.

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